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(54) Title: METHODS OF TREATMENT WITH COMPOUNDS HAVING RAR RECEPTOR SPECIFIC OR SELECTIVE ACTIVITY

(57) Abstract

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Retinoid compounds which act specifically or selectively on RARo receptor subtypes in preference over RARo and RARr receptor subtypes, possess desirable pharmaceutical properties associated with retinoids, and are particularly suitable for treatment of tumors, such as acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas and head and neck carcinomas, without having one or more undesirable side effects of retinoids, such as inducement of weight loss, mucocutaneous toxicity, skin irritation and teratogenicity.

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METHODS OF TREATMENT WITH COMPOUNDS HAVING RAR_a
RECEPTOR SPECIFIC OR SELECTIVE ACTIVITY

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the use of compounds which have specific or selective agonist like activity on RAR_{α} retinoid receptors for treatment of diseases and conditions which respond to treatment by such retinoids. More particularly the present invention is directed to the use of RAR_{α} receptor specific or selective agents for the

treatment of tumors.

12

13

2. Background Art

Compounds which have retinoid-like activity are 14 well known in the art, and are described in numerous 15 United States and other patents and in scientific publications. It is generally known and accepted in 17 the art that retinoid-like activity is useful for 18 treating animals of the mammalian species, including 19 humans, for curing or alleviating the symptoms and 20 conditions of numerous diseases and conditions. 21 other words, it is generally accepted in the art 22 that pharmaceutical compositions having a 23 retinoid-like compound or compounds as the active 24 ingredient are useful as regulators of cell 25 proliferation and differentiation, and particularly 26 as agents for treating skin-related diseases, 27 including, actinic keratoses, arsenic keratoses, 28 inflammatory and non-inflammatory acne, psoriasis, 29 ichthyoses and other keratinization and 30 hyperproliferative disorders of the skin, eczema, 31 atopic dermatitis, Darriers disease, lichen planus, 32 prevention and reversal of glucocorticoid damage 33 (steroid atrophy), as a topical anti-microbial, as 34 skin anti-pigmentation agents and to treat and

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2

reverse the effects of age and photo damage to the skin. Retinoid compounds are also useful for the

3 prevention and treatment of cancerous and

4 precancerous conditions, including, premalignant and

5 malignant hyperproliferative diseases such as

6 cancers of the breast, skin, prostate, cervix,

uterus, colon, bladder, esophagus, stomach, lung,

8 larynx, oral cavity, blood and lymphatic system,

9 metaplasias, dysplasias, neoplasias, leukoplakias

and papillomas of the mucous membranes and in the

treatment of Kaposi's sarcoma. In addition,

12 retinoid compounds can be used as agents to treat

diseases of the eye, including, without limitation,

14 proliferative vitreoretinopathy (PVR), retinal

detachment, dry eye and other corneopathies, as well

16 as in the treatment and prevention of various

17 cardiovascular diseases, including, without

18 limitation, diseases associated with lipid

metabolism such as dyslipidemias, prevention of

20 post-angioplasty restenosis and as an agent to

21 increase the level of circulating tissue plasminogen

22 activator (TPA). Other uses for retinoid compounds

23 include the prevention and treatment of conditions

24 and diseases associated with human papilloma virus

25 (HPV), including warts and genital warts, various

26 inflammatory diseases such as pulmonary fibrosis,

27 ileitis, colitis and Krohn's disease,

28 neurodegenerative diseases such as Alzheimer's

29 disease, Parkinson's disease and stroke, improper

me pituitary function, including insufficient

31 production of growth hormone, modulation of

apoptosis, including both the induction of apoptosis

and inhibition of T-cell activated apoptosis,

34 restoration of hair growth, including combination

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- therapies with the present compounds and other
- 2 agents such as Minoxidil^R, diseases associated with
- 3 the immune system, including use of the present
- 4 compounds as immunosuppressants and
- 5 immunostimulants, modulation of organ transplant
- 6 rejection and facilitation of wound healing,
- 7 including modulation of chelosis.
- United States Patent Nos. 4,740,519 (Shroot et
- 9 <u>al.</u>), 4,826,969 (<u>Maignan et al.</u>), 4,326,055
- (Loeliger et al.), 5,130,335 (Chandraratna et al.),
- 11 5,037,825 (Klaus et al.), 5,231,113 (Chandraratna et
- 12 al.), 5,324,840 (Chandraratna), 5,344,959
- (Chandraratna), 5,130,335 (Chandraratna et al.),
- 14 Published European Patent Application Nos. 0 170 105
- 15 (Shudo), 0 176 034 A (Wuest et al.), 0 350 846 A
- 16 (<u>Klaus et al.</u>), 0 176 032 A (<u>Frickel et al.</u>), 0 176
- 17 033 A (Frickel et al.), 0 253 302 A (Klaus et al.),
- 18 0 303 915 A (Bryce et al.), UK Patent Application GB
- 19 2190378 A (Klaus et al.), German Patent Application
- 20 Nos. DE 3715955 Al (Klaus et al.), DE 3602473 Al
- 21 (Wuest et al., and the articles J. Amer. Acad. Derm.
- 22 <u>15</u>: 756 764 (1986) (<u>Sporn et al.</u>), Chem. Pharm.
- 23 Bull. 33: 404-407 (1985) (Shudo et al.), J. Med
- 24 Chem. 1988 31, 2182 2192 (<u>Kagechika et al.</u>),
- 25 Chemistry and Biology of Synthetic Retinoids CRC
- 26 Press Inc. 1990 p 334 335, 354 (<u>Dawson et al.</u>),
- 27 describe or relate to compounds which include a
- 28 tetrahydronaphthyl moiety and have retinoid-like or
- 29 related biological activity.
- 30 United States Patent Nos. 4,980,369, 5,006,550,
- 5,015,658, 5,045,551, 5,089,509, 5,134,159,
- 32 5,162,546, 5,234,926, 5,248,777, 5,264,578,
- 33 5,272,156, 5,278,318, 5,324,744, 5,346,895,
- 5,346,915, 5,348,972, 5,348,975, 5,380,877,

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5,399,561, 5,407,937, (assigned to the same assignee
    as the present application) and patents and
 2
    publications cited therein, describe or relate to
 3
    chroman, thiochroman and 1,2,3,4-tetrahydroquinoline
    derivatives which have retinoid-like biological
    activity.
         United States Patent No. 4,723,028 (Shudo),
 7
    Published European Patent Application Nos. 0 170 105
 8
    (Shudo), German Patent Application No. DE 3524199 A1
 Q
    (Shudo), PCT WO 91/16051 (Spada et al.), PCT WO
 10
    85/04652 (Polus) and J. Med Chem. 1988 31, 2182 -
11
    2192 (Kagechika et al.), describe or relate to aryl
12
    and heteroaryl or diaryl substituted olephines or
13
    amides having retinoid-like or related biological
14
15
    activity.
        United States Patent Nos. 4,992,468, 5,013,744,
16
    5,068,252, 5,175,185, 5,202,471, 5,264,456,
17
    5,324,840, 5,326,898, 5,349,105, 5,391,753,
18
    5,414,007 and 5,434,173 (assigned to the same
19
   assignee as the present application) and patents and
20
   publications cited therein, describe or relate to
21
   compounds which have retinoid-like biological
22
   activity and a structure wherein a phenyl and a
23
   heteroaryl or a phenyl and a second phenyl group is
24
   linked with an olephinic or acetylenic linkage.
25
   Still further, several co-pending applications and
26
   recently issued patents which are assigned to the
27
   assignee of the present application, are directed to
28
   further compounds having retinoid-like activity.
29
        It is now general knowledge in the art that two
30
   main types of retinoid receptors exist in mammals
31
   (and other organisms). The two main types or
32
   families of receptors are respectively designated
33
   RARs and RXRs. Within each type there are subtypes;
34
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- in the RAR family the subtypes are designated RAR_{α} ,
- RAR_B and RAR_r, in RXR the subtypes are: RXR_{α} , RXB_{B} and
- 3 RXR_r. It has also been established in the art that
- 4 the distribution of the two main retinoid receptor
- 5 types, and of the several sub-types is not uniform
- 6 in the various tissues and organs of mammalian
- 7 organisms.
- It is also known in the art that the use of
- e retinoid-like compounds for the treatment of various
- diseases and conditions is not without problems or
- 11 side effects. The side effects at therapeutic dose
- 12 levels include headache, teratogenesis,
- mucocutaneous toxicity, musculoskeletal toxicity,
- 14 dislipidemias, skin irritation, headache,
- 15 hepatotoxicity, etc. These side effects limit the
- 16 acceptability and utility of retinoids for treating
- 17 disease. Research is still ongoing in the art to
- determine which of the RAR or RXR familes and within
- each family, which of the subtype or subtypes are
- 20 responsible for mediating certain therapeutic
- 21 effects, and which type or subtypes are responsible
- 22 for mediating one or more of the undesired side
- 23 effects. Accordingly, among compounds capable of
- 24 binding to retinoid receptors, specificity or
- 25 selectivity for one of the main types or families,
- 26 and even specificity or selectivity for one or more
- 27 subtypes within a family of receptors, is considered
- 28 a desirable pharmacological property. Such
- 29 selectivity or specificity is useful as a research
- 30 tool for discovering the roles of the several
- 31 receptor types and subtypes in mediating the various
- 32 effects of retinoids in biological systems, and also
- 33 as aid for designing retinoid drugs with specific
- 34 therapeutic effects and/or with reduced side effects

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- and toxicity. Along these lines, United States
- 2 Patent No. 5,324,840 describes a class of compounds
- 3 in which retinoid-like activity is accompanied by
- 4 reduced skin toxicity and reduced teratogenic
- 5 effects. United States Patent No. 5,399,586
- 6 describes the use of compounds having RXR retinoid
- 7 receptor agonist activity for the treatment of
- s mammals afflicted with tumors. United States Patent
- No. 5,455,265 describes methods of treatment of
- mammals with compounds having agonist-like activity
- on RXR receptors. Published PCT application No.
- 12 W093/11755 is also directed to the use of compounds
- which are selective RXR receptor agonists.
- The present invention provides methods of
- 15 treatment of tumors with compounds which are
- 16 specific or selective to RAR receptors.
- SUMMARY OF THE INVENTION It has been
- 18 discovered in accordance with the present invention
- 19 that retinoid-like compounds which act selectively,
- or preferably even specifically on RAR_{α} receptor
- subtypes in preference over RAR_{n} and RAR_{r} receptor
- 22 subtypes, possess desirable pharmaceutical
- 23 properties associated with retinoids, and are
- 24 particularly suitable for treatment of tumors, such
- 25 as acute monocytic leukemia, cervical carcinoma,
- 26 myeloma, ovarian carcinomas and head and neck
- 27 carcinomas, without having one or more undesirable
- 28 side effects of retinoids, such as inducement of
- 29 weight loss, mucocutaneous toxicity, skin irritation
- 30 and teratogenecity.
- Accordingly, the present invention relates to
- 32 the use of RAR $_{\alpha}$ specific or selective retinoid
- 33 compounds for the treatment of diseases and
- 34 conditions which respond to treatment by such

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- compounds, and particularly to the treatment of
- 2 tumors, primarily acute monocytic leukemia, cervical
- 3 carcinoma, myeloma, ovarian carrcinomas and head and
- 4 neck carcinomas with the \mathtt{RAR}_{lpha} specific or selective
- 5 retinoid compounds. In accordance with the present
- 6 invention the RAR_{α} selective compounds are also
- 7 particularly advantageously used for treatment of
- proliferative vitreoretinopathy (PVR) and age
- related macular degeneration (AMD).
- For the purposes of the present description a
- compound is considered RAR_{α} specific or selective if in a transactivation assay (described below) the
- compound transactivates the RAR_{α} receptors at a
- 14 significantly lower concentration than the RAR, and
- 15 RAR_r receptors. Instead of measuring
- transactivation, measuring the binding of a compound
- respectively to the three RAR receptor subtypes is
- also feasible. Binding data expressed in Kd numbers
- obtained in a binding assay (described below) are
- 20 also indicative of a compound's ability to act
- specifically or selectively on RAR_a receptors in
- 22 preference over RAR $_{\mathfrak{g}}$ and RAR $_{\mathfrak{r}}$ receptors. A compound
- 23 is considered RAR $_{\alpha}$ specific or selective for the
- 24 purposes of the present invention if the Kd number
- 25 for its binding to RAR_{α} receptors is approximately
- 26 500 times smaller than the Kd for its affinity to
- $^{\rm 27}$ ${\rm RAR}_{\rm B}$ and ${\rm RAR}_{\rm r}$ receptors.

28 BRIEF DESCRIPTION OF THE DRAWING FIGURES

- 29 Figure 1 is a graph showing the results of an RPMI
- 30 8226 cell culture assay conducted with all trans
- retinoic acid (ATRA) and two RAR_{α} selective compounds
- 32 in accordance with the present invention.
- Figure 2 is another graph showing the results of an AML 193 cell culture assay conducted with two RAR_a

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selective compounds in accordance with the present
   invention, and with two compounds which are not RAR,
    selective.
        Figure 3 is still another graph showing results
   of an AML 193 cell culture assay conducted with
   three RAR_{\alpha} selective compounds in accordance with the
   present invention and with all trans retinoic acid
7
   (ATRA).
        Figure 4 is a graph showing the proliferation of
8
   ovarian tumor cells in a cell culture assay (EDR
10
   assay) in the presence of varying concentrations of
11
   Compound 2 in accordance with the present invention.
12
        Figure 5 is a graph showing the RPE cell
13
   proliferation in the presence of all trans retinoic
14
   acid or Compound 42 in the culture medium.
15
```

Figure 6 is a graph showing the weight of a group of experimental rats which were administered for 3 days varying doses of an RAR_{α} selective compound in accordance with the present invention.

Figure 7 is a bar graph showing the weight of
a group of experimental rats at the end of a 4 day
period wherein for three days the rats were
administered varying doses of Compound 18 in
accordance with the invention;

Figure 8 is a graph showing the weight of guinea pigs which were treated with varying doses of Compound 42 for 15 days.

DETAILED DESCRIPTION OF THE INVENTIONGENERAL
EmbodimentsDefinitions regarding the chemical
compounds used in the present invention

The term alkyl refers to and covers any and all groups which are known as normal alkyl, branched-chain alkyl and cycloalkyl. The term alkenyl refers to and covers normal alkenyl, branch

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19

25

26

chain alkenyl and cycloalkenyl groups having one or

2 more sites of unsaturation. Similarly, the term

3 alkynyl refers to and covers normal alkynyl, and

4 branch chain alkynyl groups having one or more

5 triple bonds.

Lower alkyl means the above-defined broad 6 definition of alkyl groups having 1 to 6 carbons in 7 case of normal lower alkyl, and as applicable 3 to 6 8 carbons for lower branch chained and cycloalkyl Lower alkenyl is defined similarly having 2 10 to 6 carbons for normal lower alkenyl groups, and 3 11 to 6 carbons for branch chained and cyclo- lower 12 13 alkenyl groups. Lower alkynyl is also defined similarly, having 2 to 6 carbons for normal lower 14 alkynyl groups, and 4 to 6 carbons for branch 15

chained lower alkynyl groups.

The term "ester" as used here refers to and 17 covers any compound falling within the definition of that term as classically used in organic chemistry. 19 It includes organic and inorganic esters. 20 in the general formula of the preferred compounds 21 used in the invention is -COOH, this term covers the 22 products derived from treatment of this function 23 with alcohols or thioalcohols preferably with 24 aliphatic alcohols having 1-6 carbons. 25 Where the ester is derived from compounds where B is -CH2OH, this term covers compounds derived from organic 27 acids capable of forming esters including 28 phosphorous based and sulfur based acids, or 29 compounds of the formula $-CH_2OCOR_{11}$ where R_{11} is any 30 substituted or unsubstituted aliphatic, aromatic, 31 heteroaromatic or aliphatic aromatic group, 32 preferably with 1-6 carbons in the aliphatic 33 portions. 34

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Unless stated otherwise in this application, 1 preferred esters are derived from the saturated aliphatic alcohols or acids of ten or fewer carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are those derived from lower alkyl acids and alcohols. preferred are the phenyl or lower alkyl phenyl esters. Amides has the meaning classically accorded that 10 term in organic chemistry. 11 In this instance it includes the unsubstituted amides and all aliphatic 12 and aromatic mono- and di- substituted amides. 13 Unless stated otherwise in this application, 14 preferred amides are the mono- and di-substituted 15 amides derived from the saturated aliphatic radicals 16 of ten or fewer carbon atoms or the cyclic or 17 saturated aliphatic-cyclic radicals of 5 to 10 18 carbon atoms. Particularly preferred amides are 19 those derived from substituted and unsubstituted 20 lower alkyl amines. 21 Also preferred are mono- and disubstituted amides derived from the substituted 22 and unsubstituted phenyl or lower alkylphenyl 23 Unsubstituted amides are also preferred. amines. 24 Acetals and ketals include the radicals of the 25 formula-CK where K is (-OR)2. Here, R is lower 26 alkyl. Also, K may be -OR,O- where R, is lower alkyl 27 of 2-5 carbon atoms, straight chain or branched. 28 A pharmaceutically acceptable salt may be 29 prepared for any compound used in this invention 30 having a functionality capable of forming such-salt, 31 for example an acid functionality. 32 pharmaceutically acceptable salt is any salt which 33

retains the activity of the parent compound and does

- not impart any deleterious or untoward effect on the
- 2 subject to which it is administered and in the
- 3 context in which it is administered.
- 4 Pharmaceutically acceptable salts may be derived
- 5 from organic or inorganic bases. The salt may be a
- 6 mono or polyvalent ion. Of particular interest are
- 7 the inorganic ions, sodium, potassium, calcium, and
- magnesium. Organic salts may by be made with
- amines, particularly ammonium salts such as mono-,
- 10 di- and trialkyl amines or ethanol amines. Salts
- may also be formed with caffeine, tromethamine and
- 12 similar molecules. Where there is a nitrogen
- 13 sufficiently basic as to be capable of forming acid
- 14 addition salts, such may be formed with any
- inorganic or organic acids or alkylating agent such
- as methyl iodide. Preferred salts are those formed
- with inorganic acids such as hydrochloric acid,
- 18 sulfuric acid or phosphoric acid. Any of a number
- of simple organic acids such as mono-, di- or tri-
- 20 acid may also be used.
- Some of the compounds used in the present
- 22 invention may have trans and cis (E and Z) isomers.
- 23 In addition, the compounds used in the present
- 24 invention may contain one or more chiral centers and
- 25 therefore may exist in enantiomeric and
- 26 diastereomeric forms. The scope of the present
- 27 invention is intended to cover the use of all such
- 28 isomers per se, as well as mixtures of cis and trans
- 29 isomers, mixtures of diastereomers and racemic
- 30 mixtures of enantiomers (optical isomers) as well.
- Description of the Compounds Preferably Used in the
- 32 Methods of the Invention
- The retinoid-like compounds used in the methods
- 34 of treatment of the present invention are specific

or selective for RAR_{α} receptors. That a compound is

2 specific or selective to RAR_α receptors can be

3 ascertained in transactivation assays described

4 below where an RAR_{α} specific or selective compound

transactivates RAR_{α} receptors at a significantly

6 lower concentrations than RAR_{B} or RAR_{Γ} receptors. In

7 a binding assay where the ability of the compound to

bind to these receptor subtypes is measured, a

9 compound that is considered RAR_α specific or

10 selective for the purposes of the present invention

binds at least approximately 500 times stronger to

12 RAR $_{\alpha}$ receptors than to the RAR $_{\beta}$ or RAR $_{r}$ receptors.

13 Alternatively, the compound is considered RAR_a

specific or selective if in the binding assay its Kd

number is approximately in the 10^{-1} to 5 x 10^{2}

nanomolar range and the Kd number for RAR, or RAR,

17 receptors is greater than 1000 nanmolar. The latter

18 is indicated by 0.00 in the below provided Tables

where binding data (Kd numbers) for certain

20 exemplary compounds of the present invention are

21 illustrated.

Examples for RAR_α selective compounds which are preferably used in accordance with the present

invention are illustrated by Formula 1 and Formula 2

26

27

28 29

30

24 25

 $(R_3)_0$ $(R_2)_m$ $(R_2)_m$ $(R_3)_0$ $(W_1)_p$

(R₂)m

L — Y(W₂)r — B

(W₃)p

31 32

33

34

Formula 1

Formula 2

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```
where X_1 is 0 or X_1 is [C(R_1)_1]_n where n is an integer
     between 0 and 2;
          \mathbf{R}_{\text{I}} is independently H or alkyl of 1 to 6
  3
  4
     carbons;
          \mathbf{R}_{2} is independently hydrogen, or lower alkyl of
  5
     1 to 6 carbons;
  6
          R, is hydrogen, lower alkyl of 1 to 6 carbons or
 7
     F;
 8
         m is an integer having the value of 0 - 5;
 9
         o is an integer having the value of 0 - 4;
 10
         p is an integer having the value of 0 - 2;
 11
         r is an integer having the value 0 - 2;
 12
         X2 is N or CH;
 13
         Y is a phenyl or naphthyl group, or heteroaryl
14
    selected from a group consisting of pyridyl,
15
    thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
16
    thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said
17
    phenyl, naphthyl and heteroaryl groups being
18
    optionally substituted with one or two R2 groups;
19
         W, is a substituent selected independently from
20
    the group consisting of F, Br, Cl, I, fluoro
21
    substituted C_{1-6} alkyl, NO_2, and OH, with the provisos
22
23
    that:
             when the compound is in accordance with
24
   Formula 1 and Z is 0 then the sum of p and r is at
25
   least 1 and W_1 is not a fluoro group in the 3
26
   position of a tetrahydronaphthalene ring;
27
        (ii) when the compound is in accordance with
   Formula 1 and r is zero and p is 1 and W_1 is OH then
   the OH group is positioned \alpha to the L group;
        W<sub>2</sub> is a substituent selected independently from
   the group consisting of F, Br, Cl, I, fluoro
   substituted C_{1-6} alkyl, NO_2, and OH;
        W, is a substituent selected independently from
```

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the group consisting of F, Br, Cl, I, C, alkyl,
    fluoro substituted C1-6 alkyl, NO2, and OH with the
2
    proviso that when the compound is in accordance with
    Formula 2 and X, is CH and r is 0 then p is not 0 and
    at least one W, group is not alkyl;
        L is -(C=Z)-NH- or -NH-(C=Z)-
        Z is 0 or S, and
7
        B is COOH or a pharmaceutically acceptable salt
8
   thereof, COOR, CONR, R10, -CH2OH, CH2OR11, CH2OCOR11,
9
   CHO, CH(OR_{12})_2, CHOR_{13}O, -COR_7, CR_7(OR_{12})_2, CR_7OR_{13}O,
10
   where R, is an alkyl, cycloalkyl or alkenyl group
11
   containing 1 to 5 carbons, R_8 is an alkyl group of 1
12
   to 10 carbons or trimethylsilylalkyl where the alkyl
13
   group has 1 to 10 carbons, or a cycloalkyl group of
14
   5 to 10 carbons, or R<sub>s</sub> is phenyl or lower
15
   alkylphenyl, R_{i} and R_{i0} independently are hydrogen,
16
   an alkyl group of 1 to 10 carbons, or a cycloalkyl
17
   group of 5-10 carbons, or phenyl or lower
18
   alkylphenyl, R11 is lower alkyl, phenyl or lower
19
   alkylphenyl, R12 is lower alkyl, and R1, is divalent
20
   alkyl radical of 2-5 carbons.
21
        With reference to symbol X_1 in Formula 1,
22
   compounds are preferred in the methods of the
23
   present invention where X_1 is [C(R_1)_2]_n and n is 1
24
   (tetrahydronaphthalene derivatives) and also where X,
25
   is O (chroman derivatives). With reference to the
26
   symbol X2 in Formula 2, compounds are equally
27
   preferred where X2 is CH or N. When X2 is CH then
28
   the benzene ring is preferably 1, 3, 5 substituted
29
   with the L group occupying the 1 position and the W,
30
   and/or R_2 groups occupying the 3 and 5 positions.
31
   When the symbol X2 is N, then the pyridine ring is
32
   preferably 2,4,6 substituted with the L group
33
   occupying the 4 position and the W, and/or R, groups
34
```

- occupying the 2 and 6 positions.
- The R_1 groups of Formula 1 are preferably H or
- 3 CH3. The R3 group of Formula 1 is preferably H. The
- 4 group B of the preferred compounds of the invention
- 5 is COOH or a pharamceutically acceptable salt
- thereof, $COOR_8$ or $CONR_9R_{10}$, where R_8 , R_9 and R_{10} are
- 7 defined as above.
- Referring now to the W_1 and W_2 groups in Formula
- 9 1, these groups are, generally speaking, electron
- 10 withdrawing groups, which are present in the
- compounds of the invention either in the aromatic
- portion of the condensed ring system, or as a
- substituent of the aryl or heteroaryl group Y.
- Preferably a W2 group is present in the Y group, and
- 15 a W_1 group is also present in the aromatic portion of
- the condensed ring system. When the Z group is S
- 17 (thioamides) a W₁ or W₂ group does not necessarily
- have to be present in the compounds of the invention
- in accordance with Formula 1, although preferably
- at least one of the W_1 or W_2 groups is nevertheless
- 21 present. In the aryl or heteroaryl Y moiety in the
- compounds of Formula 1 and Formula 2 as well, the W_2
- group is preferably located in the position adjacent
- to the B group; preferably the B group is in para
- position in the phenyl ring relative to the "amide"
- 26 moiety, and therefore the W2 group is preferably in
- 27 meta position relative to the amide moiety. Where
- 28 there is a W₁ group present in the aromatic portion
- of the condensed ring system of the compounds of
- 30 Formula 1, it preferably occupies the 8 position of
- 31 the chroman nucleus with the Z=C-NH- group occupying
- 32 the 6 position. In tetrahydronaphthalene compounds
- of Formula 1, the Z=C-NH- group is preferably in the
- 34 2-position, and the W, group is preferably in the 4

```
position. However, when the W1 group is OH in
    compounds of Formula 1, then the OH is preferably in
  2
    the 3 position of the tetrahydronaphthalene ring.
  3
         Preferred W_1 and W_2 groups are F, NO_2, Br, I,
 4
          ClN_3, and OH. The presence of one or two
 5
    fluoro substituents in the Y group (W_2) is especially
 6
    preferred. When the Y group is phenyl, the fluoro
 7
    substituents preferably are in the ortho and ortho'
 8
    positions relative to the B group, which is
 9
    preferably COOH or COOR.
 10
         Referring now to the W<sub>3</sub> group in Formula 2, this
 11
    group is, generally speaking, also an electron
12
    withdrawing group or an alkyl group, more
13
    specifically preferred W, groups are F, NO2, Br, I,
14
    CF3, N3, and OH. Alternatively, in the phenyl or
15
    pyridyl ring (shown in Formula 2 as substituent
16
    "(W_3)_n") W_3 is an alkyl group, preferably
17
    branch-chained alkyl, such as tertiary butyl, and
18
    preferably p is 2.
19
        With reference to the symbol Y in Formula 1 and
20
    in Formula 2 as well, the preferred compounds used
21
    in the methods of the invention are those where Y is
22
   phenyl, pyridyl, 2-thiazolyl, thienyl, or furyl,
23
   more preferably phenyl. As far as substitutions on
24
   the Y (phenyl) and Y (pyridyl) groups are concerned,
25
   compounds are preferred where the phenyl group is
26
   1,4 (para) substituted by the L and B groups, and
27
   where the pyridine ring is 2,5 substituted by the L
28
29
   and B groups.
                  (Substitution in the 2,5 positions in
   the "pyridine" nomenclature corresponds to
30
   substitution in the 6-position in the "nicotinic
31
   acid" nomenclature.) In the preferred compounds of
32
   the invention there is no optional R_1 substituent
33
```

(other than H) on the Y group.

The L group of Formula 1 and of Formula 2 is preferably -(C=Z)-NH-, and Z is preferably 0. In other words, those carbamoyl or amide compounds are preferred in accordance with the present invention where the -NH-moiety is attached to the Y group.

The compounds which are presently most preferably used in the methods of treatment of the invention are shown below in Table 1 with reference to Formulas 3 and 4 and in Table 2 with reference to Formula 5.

$$V_{0}$$
 V_{0}
 V_{0

Formula 3

 R_1 W_6 CO_2R_6 W_7 W_7

Formula 4

INSDOCID: <WO 9724116A2_(>

1 2 3 5 6 7 8 Formula 5 TABLE 1 9 Compound 10 No. 11 Formula R_1 W_4 W_5 Z W_6 W_7 **R8*** 1 3 12 H H 0 F H Et 2 3 13 H H 0 F H H 3 3 14 H Br 0 F H Et 4 3 15 H Br0 F H H 5 3 16 OH H 0 F H Et 6 3 17 OH H 0 F H H 7 4 18 H H Br 0 F H Et 8 19 H H Br 0 F H H 9 20 CH₃ H Br 0 F H Et 10 21 CH₃ H \mathbf{Br} 0 F H H CH₃ 11 4 22 H CF3 0 F H Et 12 4 23 CH3 CF₃ H 0 F H H 13 24 4 CH, H N₃ 0 F H Et 14 CH₃ 25 4 H N_3 0 F H H 26 15 4 CH, CF₃ H 0 F F CH, 16 4 27 CH₃ H CF₃ 0 F F H 17 4 CH₃ 28 H I 0 F H Et 29 18 4 CH₃ H Ι 0 F H H 19 30 4 CH₃ H CH₃ 0 F H Et 20 CH₃ 31 4 CH₃ H 0 F H H 21 3 32 H H S H H Et 22 3 33 H H S H H H 23 3 H H S F H. Et

11

3

H

				19					
1	24	3		Ħ	H	s	F	Н	H
2	25	3		Н	Br	O	NO ₂	H	СН3
3	26	3		H	Br	0	NO ₂	H	Н
4	27	4	CH ₃	H	H	O	F	Ħ	Et
5	28	4	CH ₃	H	H	0	F	H	H
6	29	3		ОН	Br	0	F	H	Et
7	30	3		ОН	Br	O	F	Н	Н
8	31	3		ОН	Br	0	F	F	Ме
9	32	3		ОН	Br	0	F	F	Н
10	33	3		Н	H	0	F	F	Me

14 Compound # X2 W8 W9 W10 R*8 15 41 N H F H Et 16 42 N H F H H 17 43 N H <th>13</th> <th></th> <th></th> <th>Table</th> <th>2</th> <th></th> <th></th>	13			Table	2		
16 42 N H F H H 17 43 N H H H H H Et 18 44 N H H H H H 19 45 CH H F H Et 20 46 CH H F H H 21 47 CH OH F H Et 22 48 CH OH F H H 23 49 N H F F H H 24 50 N H F F H Me 24 50 N H F F H 25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	14	Compound #	X ₂	W_{a}	W ₉	W 10	R*
17 43 N H H H H Et 18 44 N H H H H H 19 45 CH H F H Et 20 46 CH H F H Et 21 47 CH OH F H Et 22 48 CH OH F H H 23 49 N H F F Me 24 50 N H F F Me 25 51 CH H F F Me 26 52 CH H F F Me 27 53 N H NO ₂ H Me	15	41	N	H	F	H	Et
18 44 N H H H H H 19 45 CH H F H Et 20 46 CH H F H H 21 47 CH OH F H Et 22 48 CH OH F H H 23 49 N H F F H 24 50 N H F F H 25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	16	42	N	H	F	H	Н
19 45 CH H F H Et 20 46 CH OH F H Et 21 47 CH OH F H H 22 48 CH OH F H H 23 49 N H F F Me 24 50 N H F F Me 25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	17	43	N	H	H	H	Et
20 46 CH H F H H 21 47 CH OH F H Et 22 48 CH OH F H H 23 49 N H F F Me 24 50 N H F F H 25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	18	44	N	H	Н	H	н
21 47 CH OH F H Et 22 48 CH OH F H H 23 49 N H F F Me 24 50 N H F F Me 25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	19	45	CH .	H	F	H	Et
22 48 CH OH F H H 23 49 N H F F Me 24 50 N H F F H 25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	20	46	CH	H	F	H	H
22 48 CH OH F H H 23 49 N H F F Me 24 50 N H F F H 25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	21	47	CH	ОН	F	Ħ	Et
23 49 N H F F Me 24 50 N H F F H 25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	22	48	СН	ОН	F	H	
24 50 N H F F H 25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	23	49	N	н	F	F	
25 51 CH H F F Me 26 52 CH H F F H 27 53 N H NO ₂ H Me	24	50	N	H	F	F	
26 52 CH H F F H 27 53 N H NO ₂ H Me	25	51	СН	H	F	F	
27 53 N H NO ₂ H Me	26	52	СН	H	F	F	
20 54 17	27	53	N	Н	NO,	н	
	28	54	N				

Modes of Administration

The RAR_α specific or selective compounds used in the methods of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need

- for site-specific treatment, quantity of drug to be
- administered, and numerous other considerations.
- In the treatment of dermatoses, it will
- 4 generally be preferred to administer the drug
- 5 topically, though in certain cases such as treatment
- 6 of severe cystic acne or psoriasis, oral
- 7 administration may also be used. Any common topical
- s formulation such as a solution, suspension, gel,
- o ointment, or salve and the like may be used.
- 10 Preparation of such topical formulations are well
- described in the art of pharmaceutical formulations
- as exemplified, for example, Remington's
- 13 Pharmaceutical Science, Edition 17, Mack Publishing
- 14 Company, Easton, Pennsylvania. For topical
- 15 application, these compounds could also be
- administered as a powder or spray, particularly in
- 17 aerosol form. If the drug is to be administered
- systemically, it may be confected as a powder, pill,
- tablet or the like or as a syrup or elixir suitable
- 20 for oral administration. For intravenous or
- 21 intraperitoneal administration, the compound will be
- 22 prepared as a solution or suspension capable of
- 23 being administered by injection. In certain cases,
- 24 it may be useful to formulate these compounds by
- 25 injection. In certain cases, it may be useful to
- 26 formulate these compounds in suppository form or as
- 27 extended release formulation for deposit under the
- 28 skin or intramuscular injection.
- Other medicaments can be added to such topical
- 30 formulation for such secondary purposes as treating
- 31 skin dryness; providing protection against light;
- other medications for treating dermatoses;
- 33 medicaments for preventing infection, reducing
- 34 irritation, inflammation and the like.

Treatment of dermatoses or any other indications

- 2 known or discovered to be susceptible to treatment
- 3 by retinoic acid-like compounds will be effected by
- 4 administration of the therapeutically effective dose
- of one or more compounds of the instant invention.
- 6 A therapeutic concentration will be that
- 7 concentration which effects reduction of the
- 8 particular condition, or retards it expansion. In
- 9 certain instances, the compound potentially may be
- 10 used in prophylactic manner to prevent onset of a
- n particular condition.
- A useful therapeutic or prophylactic
- 13 concentration will vary from condition to condition
- 14 and in certain instances may vary with the severity
- of the condition being treated and the patient's
- 16 susceptibility to treatment. Accordingly, no single
- 17 concentration will be uniformly useful, but will
- 18 require modification depending on the
- 19 particularities of the disease being treated. Such
- 20 concentrations can be arrived at through routine
- 21 experimentation. However, it is anticipated that in
- 22 the treatment of, for example, acne, or similar
- 23 dermatoses, that a formulation containing between
- 24 0.01 and 1.0 milligrams per mililiter of formulation
- 25 will constitute a therapeutically effective
- 26 concentration for total application. If
- 27 administered systemically, an amount between 0.01
- 28 and 5 mg per kg per day of body weight would be
- 29 expected to effect a therapeutic result in the
- 30 treatment of many disease for which these compounds
- 31 are useful.
- In the treatment of tumors a dose of
- 33 approximately 0.5 to 5 mg per kg body weight per day
- 34 is anticipated to constitute the therapeutic dose.

- Alternatively, as is performed frequently in therapy
- of malignancies, a patient is provided an initial
- 3 dose of 1 mg per kg body weight per day, and
- 4 therafter the dose is raised until a maximum
- 5 tolerated dose is attained.
- 6 Assay of RAR receptor selective biological activity
- 7 and its significance in reduced side effects and
- 8 toxicity
- As it is noted in the introductory section of
- this application for patent two main types of
- 11 retinoic acid receptors (RAR and RXR) exist in
- mammals (and other organisms). Within each type
- there are sub-types (RAR $_{\alpha}$, RAR $_{\beta}$, RAR $_{\Gamma}$, RXR $_{\alpha}$, RXR $_{\beta}$ and
- 14 RXR_r) the distribution of which is not uniform in the
- 15 various tissues and organs of mammalian organisms.
- 16 Selective binding of only one or two retinoid
- 17 receptor subtypes within one retinoid receptor
- 18 family can give rise to beneficial pharmacological
- 19 properties because of the varying distribution of
- 20 the sub-types in the several mammalian tissues or
- organs. For the above-summarized reasons, binding
- of any or all of the retinoid receptors, as well as
- 23 specific or selective activity in a receptor family,
- or selective or specific activity in any one of the
- 25 receptor subtypes, are all considered desirable
- 26 pharmacological properties.
- 27 In light of the foregoing the prior art has
- 28 developed assay procedures for testing the agonist
- 29 like activity of compounds in the RAR_{α} , RAR_{β} , RAR_{Γ} ,
- 30 RXR_a, RXR_B and RXR_r receptor subtypes. For example,
- a chimeric receptor transactivation assay which
- 32 tests for agonist-like activity in the RAR_a, RAR_B,
- 33 $RAR_{\rm r}$, and RXR_{α} receptor subtypes, and which is based
- on work published by Feigner P. L. and Holm M.

- (1989) Focus, 11 2 is described in detail in U.S.
- 2 Patent No. 5,455,265. The specification of United
- 3 States Patent No. 5,455,265 is expressly
- 4 incorporated herein by reference.
- 5 A holoreceptor transactivation assay and a
- 6 ligand binding assay which measure the ability of
- 7 compounds to bind to the several retinoid receptor
- 8 subtypes, respectively, are described in published
- 9 PCT Application No. WO WO93/11755 (particularly on
- pages 30 33 and 37 41) published on June 24,
- 11 1993, the specification of which is also
- incorporated herein by reference. A description of
- 13 the ligand binding assay is also provided below.
- 14 BINDING ASSAY
- All binding assays were performed in a similar
- 16 fashion. All six receptor types were derived from
- the expressed receptor type (RAR α , β , Γ and RXR α ,
- 18 B, F) expressed in Baculovirus. Stock solutions of
- 10 all compounds were prepared as 10mM ethanol
- 20 solutions and serial dilutions carried out into 1:1
- 21 DMSO; ethanol. Assay buffers consisted of the
- 22 following for all six receptor assays: 8% glycerol,
- 23 120mM KC1, 8mM Tris, 5mM CHAPS 4mM DTT and 0.24mM
- PMSF, pH 7.40 room temperature.
- 25 All receptor binding assays were performed in
- the same manner. The final assay volume was $250\mu l$
- 27 and contained from $10-40\mu g$ of extract protein
- 28 depending on receptor being assayed along with 5 nM
- of [3H] all-trans retinoic acid or 10nM [3H] 9-cis
- 30 retinoic acid and varying concentrations of
- 31 competing ligand at concentrations that ranged from
- 32 0 10^{-5} M. The assays were formatted for a 96 well
- 33 minitube system. Incubations were carried out at
- 4°C until equilibrium was achieved. Non-specific

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- binding was defined as that binding remaining in the
- 2 presence of 1000nM of the appropriate unlabeled
- 3 retinoic acid isomer. At the end of the incubation
- 4 period, $50\mu l$ of 6.25% hydroxyapitite was added in
- 5 the appropriate wash buffer. The wash buffer
- 6 consisted of 100mM KCl, 10mM Tris and either 5mM
- 7 CHAPS (RXR α , β , Γ) or 0.5% Triton X-100 (RAR α , β ,
- 8 F). The mixture was vortexed and incubated for 10
- minutes at 4°C, centrifuged and the supernatant
- 10 removed. The hydroxyapitite was washed three more
- it times with the appropriate wash buffer. The
- 12 receptor-ligand complex was adsorbed by the
- 13 hydroxyapitite. The amount of receptor-ligand
- 14 complex was determined by liquid scintillation
- 15 counting of hydroxyapitite pellet.
- After correcting for non-specific binding, IC₅₀
- values were determined. The IC₅₀ value is defined as
- the concentration of competing ligand needed to
- reduce specific binding by 50%. The IC_{50} value was
- 20 determined graphically from a loglogit plot of the
- 21 data. The K_d values were determined by application
- 22 of the Cheng-Prussof equation to the IC₅₀ values, the
- 23 labeled ligand concentration and the K_d of the
- 24 labeled ligand.
- 25 The results of ligand binding assay are expressed
- 26 in K_d numbers. (See <u>Cheng et al.</u> Biochemical
- 27 Pharmacology Vol. 22 pp 3099-3108, expressly
- 28 incorporated herein by reference.)
- 29 Table 3 shows the results of the ligand binding
- 30 assay for certain exemplary compounds of the
- 31 invention.

1				TABLE 3			
2			Ligand	Binding	Assay		
3	Compound	#		K _d (nane	omolar)		
4		$RAR\alpha$	RAI	RAI BA	RF	$RXR\alpha$	RXRß
5	RXRI						
6	2	1.90	480.0	0.00	0.00	0.00	0.00
7	4	1.3	0.00	0.00	0.00	0.00	0.00
8	6	3.00	0.00	0.00	0.00	0.00	0.00
9	10	24.0	0.00	0.00	0.00	0.00	0.00
10	12	14.0	0.00	0.00	0.00	0.00	0.00
11	14	52.0	0.00	0.00	0.00	0.00	0.00
12	16	51.0	0.00	0.00	0.00	0.00	0.00
13	18	16.0	0.00	0.00	0.00	0.00	0.00
14	20	57.0	0.00	0.00	0.00	0.00	0.00
15	22	15	0.00	0.00	0.00	0.00	0.00
16	24	7.5	0.00	0.00	0.00	0.00	0.00
17	26	245.0	0.00	0.00	0.00	0.00	0.00
18	28	162.0	0.00	0.00	0.00	0.00	0.00
19	30	<3.00	0.00	.0.00	0.00	0.00	0.00
20	32	2.30	0.00	0.00	0.00	0.00	0.00
21	34	9.00	0.00	0.00	0.00	0.00	0.00
22	42	14.00	0.00	0.00	0.00	0.00	0.00
23	44	19.00	0.00	0.00	0.00	0.00	0.00
24	46	26.0	0.00	0.00	0.00	0.00	0.00
25	48	77.0	0.00	0.00	0.00	0.00	0.00
26	50	62.0	0.00	0.00	0.00	0.00	0.00
27	52	87.0	0.00	0.00	0.00	0.00	0.00
28	54	94.0	0.00	0.00	0.00		
29	TTNPI	3 ¹ 72	5	36	5		
30	0.00 indi	cates v	alue gre	eater th	an 1000	nM (nan	omolar)
31	0.00 indicates value greater than 1000nM (nanomolar) TTNPB is a well known prior art retinoid $(4-(E)-2-$						
32							
33							
34							

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As it can be seen from the foregoing data, the compounds used in accordance with the present invention specifically or selectively bind to RAR, 3 retinoid receptors. It has been discovered in accordance with the present invention that this 5 unique type of selectivity allows the compounds to 6 retain beneficial retinoid-like properties while 7 reduces certain side effects and toxicity. 8 specifically, certain in vitro cell culture assays are described below, in which the ability of the RAR, 10 specific or selective compounds to significantly 11 inhibit the growth of cancer cells is demonstrated. 12 CANCER CELL LINE ASSAYS 13 MATERIALS AND METHODS 14 Hormones 15 All trans-retinoic acid (t-RA) (Sigma Chemicals 16 Co., St. Louis, MO) was stored at -70°C. Prior to 17 18 each experiment the compound was dissolved in 100% ethanol at 1 mM and diluted in culture medium 19 immediately before use. All experiments were 20 performed in subdued light. Controls were assayed 21 using the same concentration of ethanol as present 22 in the experimental plates and this concentration of 23 diluent had no effect in either assay. 24 Cells and Cell Culture 25 The cell lines, RPMI 8226, ME-180 and AML-193 26 were obtained from the American Type Culture 27 Collection (ATCC, Rockville, MD). RPMI 8226 is a 28 human hematopoietic cell line obtained from the 29 peripheral blood of a patient with multiple myeloma. 30 The cells resemble the lymphoblastoid cells of other 31 human lymphocyte cell lines and secrete α-type light 32 chains of immunoglobulin. RPMI-8226 cells are grown 33

in RPMI medium (Gibco) supplemented with 10% fetal

- bovine serum, glutamine and antibiotics. The cells
- were maintained as suspension cultures grown at 37°C
- 3 in a humidified atmosphere of 5% CO2 in air. The
- 4 cells were diluted to a concentration of $1 \times 10^5/ml$
- 5 twice a week.
- 6 ME-180 is a human epidermoid carcinoma cell line
- derived from the cervix. The tumor was a highly
- s invasive squamous cell carcinoma with irregular cell
- e clusters and no significant keratinization. ME-180
- 10 cells were grown and maintained in McCoy's 5a medium
- (Gibco) supplemented with 10% fetal bovine serum,
- 12 glutamine and antibiotics. The cells were
- maintained as monolayer cultures grown at 37°C in a
- humidified atmosphere of 5% CO2 in air. The cells
- were diluted to a concentration of 1 x $10^5/ml$ twice a
- 16 week.
- 17 AML-193 was established from the blast cells
- 18 classified as M5 Acute Monocyte Leukemia. The
- 19 growth factor, granulocyte colony-stimulation factor
- 20 (GM-CSF) was required to establish this cell line
- 21 and growth factors are necessary for its continuous
- 22 proliferation in chemically defined medium. AML-193
- 23 cells were grown and maintained in Iscove's modified
- 24 Dulbecco's medium supplemented with 10% fetal bovine
- 25 serum, glutamine and antibiotics with $5\mu g/ml$ insulin
- 26 (Sigma Chemical Co.) and 2 ng/ml rh GM-CSF (R and D
- 27 Systems). The cells were diluted to a concentration
- of 3 x $10^5/\text{ml}$ twice a week.
- 29 Incorporation of ³H-Thymidine
- The method used for determination of the
- incorporation of radiolabeled thymidine was adapted
- 32 from the procedure described by Shrivastav et al.
- 33 RPMI-8226 cells were plated in a 96 well round
- 34 bottom microtiter plate (Costar) at a density of

- 1,000 cells/well. To appropriate wells, retinoid
- test compounds were added at the final 3
- concentrations indicated for a final volume of 150
- The plates were incubated for 96 hours at
- 37°C in a humidified atmosphere of 5% CO2 in air. 6
- Subsequently, 1 μ Ci of $[5'-^3H]$ -thymidine (Amersham, 7
- U.K. 43 Ci/mmol specific activity) in 25 μ l culture
- medium was added to each well and the cells were 9
- incubated for an additional 6 hours. The cultures
- were further processed as described below. 10
- ME-180 wells, harvested by trypsinization were 11 12
- plated in a 96 well flat bottom microtiter plate 13
- (Costar) at a density of 2,000 cells/well.
- cultures were treated as described above for RPMI 14
- 8226 with the following exceptions. After 15
- incubation with thymidine the supernatant was 16 17
- carefully removed, and the cells were washed with a 18
- 0.5 mM solution of thymidine in phosphate buffered 19
- saline. ME180 cells were briefly treated with $50\mu l$ 20
- of 2.5% trypsin to dislodge the cells from the 21
- plate.
- 22 AML-193 cells were plated in a 96 well round 23
- bottom microtiter plate (Costar) at a density of 24
- 1,000 cells/well. To appropriate wells, retinoid 25
- test compounds were added at the final
- concentrations indicated for a final volume of 150 26 27
- μ l/well. The plates were incubated for 96 hours at 28
- 37°C in a humidified atmosphere of 5% CO2 in air. 29
- Subsequently, 1 μ Ci of $[5'-^3H]$ -thymidine (Amersham, 30
- U.K., 43 Ci/mmol specific activity) in 25 μ l culture 31
- medium was added to each well and the cells were
- incubated for an additional 6 hours. 32
- The cell lines were then processed as follows: 33 34
- the cellular DNA was precipitated with 10%

- 1 trichloroacetic acid onto glass fiber filter mats
- 2 using a SKATRON multi-well cell harvester (Skatron
- 3 Instruments, Sterling VA). Radioactivity
- 4 incorporated into DNA, as a direct measurement of
- 5 cell growth, was measured by liquid scintillation
- 6 counting. The numbers represent the mean
- 7 disintegrations per minute of incorporated thymidine
- 8 from triplicate wells ± SEM.
- The graph of Figure 1 of the appended drawings
- shows that in the above described RPMI 8226 cell
- (malignant myeloma) culture assay Compounds 4 and 12
- 12 (two exemplary compounds used in accordance with
- this invention) inhibited the growth of these
- 14 malignant cells, substantially as well as a
- comparison compound, all trans retinoic acid (ATRA).
- 16 The graph of Figure 1 also demonstrates that whereas
- in a low concentration range $(10^{-12} \text{ to approximately})$
- $18 ext{ } 10^{-9}$) all trans retinoic acid (ATRA) actually
- 19 facilitates growth of these cells, the RAR_{α} selective
- 20 Compounds 4 and 12 of the present invention do not
- 21 stimulate but rather already in this low
- 22 concentrations inhibit the growth of these malignant
- 23 cells.
- The graph of Figure 2 shows that in the above
- 25 described AML 193 (acute monocytic leukemia) cell
- culture assay Compounds 22 and 42 in accordance with
- 27 this invention inhibited the growth of these
- 28 malignant cells. Two other compounds for which data
- 29 are also shown in this graph are designated AGN
- 30 193090 and AGN 193459. (An AGN number is an
- arbitrary designation number used by the corporate
- 32 assignee of the present invention.) The compounds
- 33 AGN 193090 and AGN 193459 are not RAR_{α} selective.
- 34 These compounds respectively are

- 4-[(8-cyano-5,6-dihydro-5,5-dimethylnaphth-2-yl)ethy
- 2 nyl]benzoic acid, and
- 3 4-[(5,6-dihydro-5,5-dimethylnaphth-7(6H)-8-(1-2,2-di
- 4 methylpropylidene)naphth-2-yl)ethynyl]benzoic acid,
- s and their Kd values for RAR_{α} , RAR_{β} and RAR_{γ} receptors
- 6 are 109, 34, 77 and 6, 2, 7, respectively. The
- 7 graph of Figure 2 demonstrates that the RAR a
- s selective or specific compounds inhibit the
- malignant cell growth at low concentrations where
- the pan agonist AGN 193090 and AGN 193459 compounds
- do not inhibit but rather at these low
- 12 concentrations even stimulate such cell growth.
- Figure 3 is another graph showing the results of
- an AML-193 cell culture assay, where Compounds 4, 12
- and 18 in accordance with the present invention, and
- 16 all trans retinoic acid (ATRA) were tested. The
- 17 data show that the RAR selective compounds reduce
- 18 cell proliferation at low concentrations whereas
- 19 ATRA at the same low concentration actually promotes
- 20 cell proliferation.
- In another line of assays the effect of the
- 22 retinoid compounds is tested against cells obtained
- 23 from solid tumors of patients. This EDR assav is
- 24 described below as follows:
- 25 Freshly resected solid tumor biopsies were
- 26 received within 24 hours of surgery. Species were
- 27 processed for assay after retaining a portion of the
- 28 tumor for paraffin embedding and histopathologic
- 29 confirmation of specimen viability and tissue
- 30 diagnosis. The remaining specimen was dissociated
- into small fragments using sterile scissors. The
- 32 small tissue fragments were then exposed to
- 33 collagenase and DNAase for 2 hours with mixing a CO2
- 34 incubator in order to release the tumor cells from

The resulting cell the connective tissue stroma. suspension was washed, and cell counts determined Tumor cells were from a cytospin preparation. resuspended at 40,000 cells per ml in 0.3% agarose in RMPI 1640 supplemented with 15% FCS, glutamine 5 and antibiotics, and 0.5 ml were plated into each 6 well of a 24 well plate over 0.5 ml layer of 0.5% 7 These culture conditions prevent cell agarose. R adherence, thereby allowing only transformed cells to proliferate. Additionally, the cells grow into 10 three dimensional spheroids, recapitulating their in 11 vivo morphology. 12 Retinoid drugs were added 24 hours after plating 13 to insure specimen reequilibration to a growth 14 environment after the rigors of transport and 15 processing. Cells were grown for four days in the 16 presence of drug, with 3H-thymidine (5 uCi/ml) added 17 48 hours prior to harvest to insure adequate 18 labeling of proliferating cells. After the 19 agarose-cell suspension was liquefied at 90°C, cells 20 were harvested onto glass fiber filters, which were 21 counted in 5 ml scintillation fluid using a Beckman 22 6500 liquid scintillation counter. 23 Results are reported as fraction of untreated 24 control cell proliferation. Treatment groups were 25 performed in duplicate or triplicate, while the 26 controls were performed in quadruplicate. 27 The graph of Figure 4 shows the effect of 28 Compound 2 on ovarian tumors obtained from 4 29 patients, and demonstrates that the compound inhibits this tumor cell proliferation in a 31 concentration dependent manner.

32 It will be understood by those skilled in the 33 art, that the ability of the RAR_{α} selective compounds 34

to significantly inhibit growth of malignant cells 1 in the above described assays is an indication that 2 these compounds can be administered with beneficial effect to tumor bearing mammals (including humans) for the treatment of tumors, particularly acute 5 monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas and head and neck carcinomas. It has also been discovered in accordance with the present invention that the proliferation of retinal pigment epithelium cells is inhibited by RAR_a 10 selective compounds. By way of background it is 11 noted that after retinal detachment the retinal 12 pigment epithelium (RPE) becomes dedifferentiated, 13 proliferates and migrates into the subretinal space 14 (Campochiaro et al., Invest. Opthal & Vis. Sci. 15 32:65-72 (1991)). Such processes therefore have an 16 impact upon the success of retinal reattachment 17 RAR agonists such as all-trans-retinoic procedures. 18 acid (ATRA) exhibit an antiproliferative effect upon 19 the growth rate of primary human RPE cultures 20 (Campochiaro et al., ibid) and have been shown to 21 decrease the incidence of retinal detachment after 22 retinal reattachment surgery in human studies 24 (Fekrat et al., Opthamology 102:412-418 (1994)). The graph of Figure 5 shows the concentration 25 dependent inhibitory effect of all trans retinoic 26 acid (ATRA) and of Compound 42 on RPE proliferation 27 in an assay procedure which is described below. 28 Analysis of primary RPE cultures 29 Primary cultures of human retinal pigment 30 epithelium (RPE) were established from eyes as 31

Primary cultures of human retinal pigment
epithelium (RPE) were established from eyes as
previously described, (Campochiaro et al., Invest.
Opthal & Vis. Sci. 32:65-72 (1991)). 5 X 10⁴ Cells
were plated in 16-mm wells of 24-well multiwell

- plates in Dulbecco's modified Eagle's medium (DMEM
- 2 Gibco) containing 10% fetal bovine serum (FBS).
- 3 Cells were treated with ethanol alone (control),
- 4 ATRA $(10^{-10}$ to 10^{-6} M) in ethanol, and Compound 42
- $_{5}$ (10⁻¹⁰ to 10⁻⁶ M) in ethanol. Cells were fed with
- 6 fresh media containing the appropriate
- 7 concentrations of these compounds every two days for
- 8 a total of six days treatment. Cells were removed
- 9 from the plates via treatment with trypsin and the
- number of cells were counted with an electronic cell
- ounter. As it can be seen in Figure 5 treatment of
- primary RPE cells with ATRA and with Compound 42
- both led to a dose dependent decrease in RPE cell
- 14 proliferation.
- The effect of topically administering to
- experimental hairless mice RAR_{α} selective retinoid
- 17 compounds in accordance with the present invention
- 18 was also evaluated in a topical skin irritation
- assay, using the RAR $_{\alpha}$ selective Compound 18 of the
- 20 invention. More particularly, skin irritation was
- 21 measured on a semi-quantitative scale by the daily
- 22 subjective evaluation of skin flaking and abrasions.
- 23 A single number, the topical irritation score,
- 24 summarizes the skin irritation induced in an animal
- 25 during the course of an experiment. The topical
- 26 irritation score is calculated as follows. The
- 27 topical irritation score is the algebraic sum of a
- 28 composite flaking score and a composite abrasion
- 29 score. The composite scores range from 0-9 and 0-8
- 30 for flaking and abrasions, respectively, and take
- into account the maximum severity, the time of
- onset, and the average severity of the flaking and
- 33 abrasions observed.
- The severity of flaking is scored on a 5-point

scale and the severity of abrasions is scored on a

2 4-point scale, with higher scores reflecting greater

- 3 severity. The maximum severity component of the
- 4 composite scores would be the highest daily severity
- s score assigned to a given animal during the course
- 6 of observation.

For the time of onset component of the composite score, a score ranging from 0 to 4 is assigned as follows:

10

12 13 Time to Appearance of Flaking or Abrasions of Severity 2 or greater

14	(days)	Time of Onset Score
15	· · · · · · · · · · · · · · · · · · ·	
16	8	0
17	6-7	1
18	5	2
19	3-4	3
20	1-2	4

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The average severity component of the composite score is the sum of the daily flaking or abrasion scores divided by the number of observation days. The first day of treatment is not counted, since the drug compound has not had an opportunity to take effect at the time of first treatment.

To calculate the composite flaking and abrasion scores, the average severity and time of onset scores are summed and divided by 2. The result is added to the maximal severity score. The composite flaking and abrasion scores are then summed to give the overall topical irritation score. Each animal receives a topical irritation score, and the values

- are expressed as the mean + SD of the individual
- 2 scores of a group of animals. Values are rounded to
- 3 the nearest integer.
- Thus, female hairless mice [Crl:SKH1-hrBR] (8-12
- 5 weeks old, n=4) were treated topically for 5
- 6 consecutive days with Compound 18 in doses expresed
- 7 in nanomol/25 g, which is particularly given in
- 8 Table 4. Treatments are applied to the dorsal skin
- 9 in a total volume of 4 ml/kg (-0.1 ml). Mice were
- observed daily and scored for flaking and abrasions
- up to and including 3 days after the last treatment,
- 12 <u>i.e.</u>, day 8.

14

15

32

Table 4

Eight Day Topical Assay in Hairless Mice of Compound 18

16 Dose Mortality Body Weight Flaking Abrasion

17 Composite

18		(out of 4) % gain or	Score	Score	Score	
19	(loss)						
20							
21	100	0	8 ± 7	0	1	1 ± 1	
22							
23	1000	0	4 ± 1	1	1	2 ± 0	
24						·	
25	of TINPB						
26							
27	0.9	0	5 ± 2	. 5	3	8 ± 2	
28							
29	2.7	0	(4 ± 3)	6	3	9 ± 2	
30	-						
31	9	0	(11 ± 3)	. 7	5	11 ± 2	
			•	-	. ~	 2	

These data show that the RAR_{α} selective compound causes virtually no skin irritation and no weight

- loss up to 1000 nmol/25g in the test model. For
- 2 comparison it should be noted that the well known
- 3 prior art retinoid compound
- 4 4-(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnapht
- 5 halen-2-yl)propen-1-yl)benzoic acid (TTNPB), which
- is not RAR_{α} selective, causes much more serious skin
- 7 irritation in the above-noted test, as is shown in
- the foregoing table.
- Another important advantage of administering
- 10 RAR $_{\alpha}$ selective retinoid compounds to a mammal lies in
- the significantly reduced teratogenic potency of the
- 12 RAR $_{\alpha}$ selective compounds compared to many other
- retinoids, as measured by a chondrogenesis
- 14 suppression bioassay. This assay is performed as
- 15 follows:
- High-density "spot" cultures of limb bud
- mesenchymal cells are used to compare the ability of
- various concentrations of test drugs to suppress
- chondrogenic differentiation as a bioassay.
- 20 Forelimb buds of mouse embryos on day 12 of
- gestation (54 \pm 2 somites) are dissociated in a
- 22 trypsin-EDTA solution, and the resultant single-cell
- 23 suspension is plated as $20-\mu l$ spots (200,000
- 24 cells/spot) on plastic culture dishes. Retinoid
- concentrations ranging from 0.3 ng/ml to 3 μ g/ml (1
- $_{26}$ nM-10 μ M) are added to the culture medium (Eagle's
- 27 MEM + 10% fetal bovine serum, GIBCO) 24 hours after
- 28 initial plating. Control cultures receive only the
- 29 vehicle (ethanol, concentration ≤ 1% by vol);
- 30 Retinoic acid is used as a positive control in
- 31 another set of cultures.
- The cultures are terminated 96 hours after
- 33 plating, at which time the medium is removed and the
- 34 cells are fixed for 1 hour in 10% formalin

	37					
1	containing 0.5% cetylpyridinium chloride. The					
2						
3	hour in 0.5% Alcian blue solution at pH 1.0,					
4	differentiated in 3% acetic acid, and then					
5	dehydrated in ethanol and scored for chondrogenesis					
6	under the microscope. An absence or reduction in					
7	the number of cartilage nodules in stained cultures					
. 8	as compared with control cultures is taken as a					
9	measure of suppression of chondrogenesis. The					
10	number of cartilage nodules stained in the whole					
11.	spot, mean number of nodules, and standard					
12	deviations are calculated for four replicate					
13	cultures per treatment. The median concentration					
. 14	causing a 50% inhibition of chondrogenesis compared					
15	with controls (IC ₅₀) is calculated by logarithmic					
16	curve fitting of the dose-response data. The IC ₅₀					
17	values are expressed in nanogram per mililiter					
18	(ng/ml) units. An IC ₅₀ value of greater					
19	concentration in this assay signifies lesser					
20	teratogenecity. Table 5 indicates the results					
21	obtained in this assay for Compounds 10, 18, and 42					
2 2	in accordance with the present invention, as well as					
23	for comparison with all trans retinoic acid (ATRA)					
24	and 4-(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetra-					
25	methylnaphtha-len-2-yl)propen-1-yl)benzoic acid					
26	(TTNPB).					
27						
28	Table 5					
29	Compound					

20		Table 5	
29	Compound]	C ₅₀ (ng/ml)
30	10		250
31	18		220
32	42		65
33	ATRA		5,5
34	TTNPB		0.01

As it can be seen the compounds used in 1 accordance with the present invention are less 2 teratogenic than all trans retinoic acid and significantly (of the 10' order of magnitude) less 4 teratogenic than the prior art TTNPB compound. 5 Weight loss or gain that experimental animals experience upon administration of retinoid compounds 7 is another test of the drug's toxicity, with significant weight loss at relatively low doses 9 indicating a significant toxic side effect of the 10 In one experiment, groups of 5 rats were retinoid. 11 treated with varying doses (administered in corn 12 oil) of a test retinoid for 3 days. The rats were 13 euthanized 24 hours after the last dose. 14 The graph of Figure 6 shows the average weight of each group 15 of rats treated with a daily dose of 10, 30, and 90 16 $\mu \text{mol/kg/day}$ of Compound 42, as well as the average 17 weight of a group of control rats which were not 18 given the retinoid. As it can be seen, the RAR_{α} 19 selective Compound 42 caused virtually no weight 20 loss, as compared to the control, except in a very 21 high dose (90 μ mol/kg/day). 22 The graph of Figure 7 shows the weight of the rats on the fourth day (24 23 hours after last administration of retinoid) in a 24 similar test with varying doses of Compound 18, with 25 a zero dose indicating the control. As it can be 26 seen, this RAR selective retinoid caused virtually 27 no weight loss even in the high dose of 90 28 μ mol/kg/day. It is noteworthy that in similar tests 29 TTNPB, which binds to all three RAR receptor 30 subtypes (see Table 3) causes very significant 31 weight loss. In this experiment involving the rats 32 treated with Compound 42, significant mucocutaneous 33

toxicity was not observed.

- In another experiment three-week old male Hartley guinea pigs were implanted intraperitonially 2 with osmotic pumps containing 20 % DMSO/80 3 polyethylene glycol (vehicle) or Compound 42 at 4 concentrations of 4.4, 13.3 or 40 mg/ml in vehicle. 5 Based on the initial body weights and known pumping rate, approximate doses of 0, 2, 6, and 18 mg/kg/day 7 doses of Compound 42 are estimated. Body weights and clinical observations were recorded at least every other day for 14 days post-implantation. 10 guinea pigs were euthanized after 14 days, and the 11 pumps were examined for possible failure. 12 The graph of Figure 8 shows the weight of the animals involved 13 in this experiment over the course of 15 days. 14 it can be seen from the graph, the lower and middle 15 doses of the RAR_{α} selective retinoid compound 16 (Compound 42) caused no, or only statistically 17 insignificant depression of weight gain, relative to 18 the control animals. Significant depression of 19 weight gain was observed only in the high dose 20 (18mg/kg/day) of Compound 42. Importantly, no signs 21 of mucocutaneous toxicity were observed at any dose 22 of Compound 42 in this experiment. 23 The foregoing, markedly reduced mucocutaneous toxicity observed 24 when animals are treated with RAR, selective 25 compounds in accordance with the present invention, 26 is a significant advantage, because mucocutaneous 27 toxicity is the major and most irksome retinoid side 28 effect or toxicity in human patients. 29 Synthetic Methods for Preparing the Preferred 30 Examples of RAR, Selective Compounds of the Invention 31 General structure of the compounds which are preferably used in the methods of treatment of the
- 32 33 present invention are shown above in Formula 1 and 34

- Formula 2. These compounds can be made by the
- 2 synthetic chemical pathways illustrated here. The
- 3 synthetic chemist will readily appreciate that the
- 4 conditions set out here are specific embodiments
- 5 which can be generalized to any and all of the
- 6 compounds represented by these formulas.
- Generally speaking the process of preparing
- s compounds preferably used in the methods of the
- 9 invention in accordance with Formula 1 involves the
- 10 formation of an amide by the reaction of a compound
- of the general Formula 6 with a compound of general
- Formula 7, or by the reaction of a compound of
- 13 general Formula 6a with a compound of general
- 14 Formula 7a. Similarly, the process of preparing
- 15 compounds in accordance with Formula 2 involves the
- 16 formation of an amide by the reaction of a compound
- of the general Formula 8 with a compound of general
- 18 Formula 7, or by the reaction of a compound of
- 19 general Formula 8a with a compound of general
- 20 Formula 7a.
- A compound of Formula 6 is an acid or an
- 22 "activated form" of a carboxylic acid attached to
- 23 the aromatic portion of a tetrahydronaphthalene, (X1
- $= [C(R_1)_2]_n$ and n is 1), dihydroindene $([C(R_1)_2]_n$ where
- n is 0) or chroman (X_1 is 0) nucleus. The carboxylic
- 26 acid, or its "activated form" is attached to the 2
- or 3 position of the tetrahydronaphthalene, and to
- 28 the 6 or 7 position of the chroman moieties. In the
- 29 compounds preferably used in accordance with the
- 30 invention the attachment is to the 2 position of
- 31 tetrahydronaphthalene and to the 6 position of
- 32 Chroman.
- 33 The term "activated form" of the carboxylic acid
- 34 should be understood in this regard as such

- derivative of the carboxylic acid which is capable
- of forming an amide when reacted with a primary
- 3 amine of Formula 7. In case of the "reverse amides"
- 4 the activated form of a carboxylic acid is a
- s derivative (Formula 7a) that is capable of forming
- 6 an amide when reacted with a primary amine of
- 7 Formula 6a. This, generally speaking, means such
- 8 derivatives of a carboxylic acid which are normally
- 9 known and used in the art to form amide linkages
- with an amine. Examples of suitable forms or
- derivatives for this purpose are acid chlorides,
- 12 acid bromides, and esters of the carboxylic acid,
- 13 particularly active esters, where the alcohol moiety
- of the ester forms a good leaving group. Presently
- most preferred as reagents in accordance with
- 16 Formula 6 (or Formula 7a) are acid chlorides (X, is
- 17 Cl). The acid chlorides of Formula 6 (or of Formula
- 18 7a) can be prepared by traditional methods from the
- corresponding esters (X, is for example ethyl) by
- 20 hydrolysis and treatment with thionyl chloride
- 21 (SO₂Cl). The acid chlorides of Formula 6 (or of
- 22 Formula 7a) can also be prepared by direct treatment
- of the carboxylic acids with thionyl chloride, where
- 24 the carboxylic acid, rather than an ester thereof is
- 25 available commercially or by a known synthetic
- 26 procedure. The acid chlorides of Formula 6 (or of
- 27 Formula 7a) are typically reacted with the amine of
- 28 Formula 7 (or amine of Formula 6a) in an inert
- 29 solvent, such as methylene chloride, in the presence
- 30 of an acid acceptor, such as pyridine.
- 31 The carboxylic acids themselves in accordance
- with Formula 6 (or Formula 7a) are also suitable for
- 33 amide formation when reacted with an amine, a
- 34 catalyst (4-dimethylaminopyridine) in the presence

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of a dehydrating agent, such as
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- 2 dicyclohexylcarbodiimide (DCC) or more preferably
- 3 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
- 4 hydrochloride (EDC).
- 5 The carboxylic acids or the corresponding esters
- of Formula 6, are generally speaking, prepared as
- 7 described in the chemical scientific or patent
- 8 literature and the literature procedures for their
- 9 preparation may be modified, if necessary, by such
- o chemical reactions or processes which per se are
- 11 known in the art. For example, generally speaking,
- 12 2,2, 4,4 and/or 2,2,4,4-substituted chroman
- 6-carboxylic acids and chroman 7-carboxylic acids
- 14 are available in accordance with the teachings of
- United States Patent Nos. 5,006,550, 5,314,159,
- 16 5,324,744, and 5,348,975, the specifications of
- which are expressly incorporated herein by
- reference. 5,6,7,8-Tetrahydronaphthalene-2-
- 19 carboxylic acids are, generally speaking, available
- 20 in accordance with the teachings of United States
- Patent No. 5,130,335, the specifications of which is
- 22 expressly incorporated herein by reference.
- 23 The foregoing general description of the
- reactions which lead to formation of the amides of
- 25 Formula 1 is also, generally speaking, applicable to
- 26 the formation of the amides of Formula 2. The
- 27 reagents which are used in accordance with the
- 28 general principles mentioned above for the formation
- of amide compounds of Formua 2 are: activated forms
- 30 of a carboxylic acids shown in Formula 8 and in
- 31 Formula 7a, and the amines of Formula 7 and of
- 32 Formula 8a.

Formula 6a

1
2
3
4
5
$$(R_3)$$
0
 (R_2) m
 (R_2) m
 (R_2) m
 (R_3) 0
 11
12
13
14
15
$$(R_3)o$$
 $(R_3)o$
 $(W_1)p$
 $(W_2)r$
 R_1
 $(R_2)m$
 NH_2
 $(W_3)O$
 $(W_2)r$
 R_3

Formula 7a

Formula 8a Formula 8a

The carboxylic acids or the corresponding esters of Formula 8, are generally speaking, prepared as described in the chemical scientific or patent literature and the literature procedures for their preparation may be modified, if necessary, by such chemical reactions or processes which per se are known in the art.

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Reaction Scheme 1

33

34

OMO.

Reaction Scheme 2

34

Reaction Scheme 2 (continued)

```
Reaction Schemes 1 and 2 provide examples for
 1
    the synthesis of derivatives of 5,6,7,8-tetrahydro-
 2
    5,5,8,8-tetramethyl-naphthalene-2-carboxylic acid,
 3
    which are within the scope of Formula 6 and which
    are reacted with an amine of Formula 7 to provide
    (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-
 6
    2-yl)carbamoyl derivatives within the scope of
 7
                Thus, as is shown in Reaction Scheme 1,
    Formula 1.
    ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-
 9
    naphthalene-2-carboxylate (Compound A) is nitrated
10
    to provide the corresponding 3-nitro compound
11
                   The nitro group of Compound B is
    (Compound B).
12
    reduced to provide the corresponding 3-amino
13
   compound (Compound C) which is described in the
14
   publication Lehmann et al. Cancer Research, 1991,
15
               Ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetra-
    51, 4804.
16
   methyl-3-amino-naphthalene-2-carboxylate (Compound
17
   C) is brominated to yield the corresponding 4-bromo
18
   derivative (Compound D), which is converted by
19
   treatment with isoamylnitrite and reduction with
20
   H<sub>3</sub>PO<sub>2</sub>, to ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetra-
21
   methyl- 4-bromonaphthalene-2-carboxylate (Compound
22
        Saponification of Compound E yields
23
   5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-bromonaphth
24
   alene-2-carboxylic acid (Compound F) which is used
25
   as a reagent in accordance with Formula 6.
26
   5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-aminonaphth
27
   alene-2-carboxylate (Compound C) is also diazotized
28
   and reacted with HBF4 to provide ethyl
29
   5,6,7,8-tetrahydro-5,5,8,8-tetra-methyl-3-fluoronaph
30
   thalene-2-carboxylate (Compound G) which serves
31
   either per se or after saponification as a reagent
32
   in accordance with Formula 6.
```

5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-

- hydroxynaphthalene (Compound H, available in
- accordance with the publication Krause Synthesis 2
- 1972 140), is the starting material in the example
- shown in Reaction Scheme 2. Compound H is
- brominated to provide the corresponding 3-bromo
- compound (Compound I) which is thereafter protected
- in the hydroxyl function by treatment with 7
- methoxymethyl chloride (MOMCl) to yield
- 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxymet-
- hoxy-2-bromonaphthalene (Compound J). Compound J is 10
- reacted with \underline{t} -butyllithium and carbon dioxide to 11
- provide the corresponding carboxylic acid (Compound 12
- K) from which the methoxymethyl protecting group is 13
- removed by acid to give 14
- 5,6,7,8-tetrahydro-5,5,8,8-tetra-15
- methyl-2-hydroxynaphthalene-3-carboxylic acid
- (Compound L). Compound L is brominated to yield 17
- 5,6,7,8-tetrahy-18
- dro-5,5,8,8-tetramethyl-1-bromo-2-hydroxynaphthalene 19
- -3-carboxylic acid (Compound M). Compound L and 20
- Compound M serve as reagents in accordance with 21
- Formula 6. The hydroxy group of Compound M is 22
- protected for further transformations with
- methoxymethyl chloride (MOMCl) in the presence of 24
- base, yielding 5,6,7,8-tetrahydro-5,5,8,8-25
- tetramethyl-1-bromo-2-methoxymethoxynaphthalene-3-ca 26
- rboxylic acid (Compound N). 27

30

31

32

33

1) SOCI₂ 2) C₂H₅OH 3) HNO₃/H₂SO₄ $\omega_2 \varepsilon_2 H_5$ CO₂H NO2 Compound O Compound W .CO₂H ,CO₂H ICI HOAc Compound O Compound X

Reaction Scheme 3

Compound A1

Reaction Scheme 4

Compound Z

CO2H

Shroot, B.

Br₂/HOAc

U. S. Patent 5,059,621

CO₂H

Compound B1

Reaction Scheme 5

- Reaction Schemes 3, 4 and 5 provide examples for
- the synthesis of derivatives of 2,2,4,4 and
- 3 4,4-substituted chroman-6-carboxylic acids which can
- 4 serve as reagents in accordance with Formula 6 for
- 5 the synthesis of the carbamoyl (amide) compounds
- 6 within the scope of the present invention. Thus,
- 7 referring now to Reaction Scheme 3,
- 8 2,2,4,4-tetramethylchroman-6-carboxylic acid
- 9 (Compound O, see U. S. Patent No. 5,006,550) is
- 10 brominated with bromine in acetic acid to yield the
- corresponding 8-bromo derivative (Compound P).
- 12 Compound P is converted to the acid chloride by
- 13 treatment with thionyl chloride, and the resulting
- 14 acid chloride is suitable for reaction with an amine
- of Formula 3 to provide the carbamoyl (amide)
- 16 compounds of the invention. The acid chloride is
- 17 also reacted with an alcohol (methanol) in the
- 18 presence of base to yield the corresponding ester,
- methyl 2,2,4,4-tetramethyl-8-bromochroman-6-
- 20 carboxylate (Compound R). The bromo function of
- 21 Compound R is converted to a trifluoromethyl
- 22 function by treatment with sodium trifluoroacetate
- 23 in the presence of cuprous iodide catalyst and
- 24 1-methyl-2-pyrrolidinone (NMP), and the carboxylate
- 25 ester group is saponified to yield
- 2, 2, 4, 4-tetramethyl-8-trifluoromethylchroman-6-carbo
- 27 xylic acid (Compound S). Compound S is within the
- 28 scope of Formula 6 and is suitable per se or as the
- 29 acid chloride or in other "activated" form to react
- with the amines of Formula 7 to yield the carbamoyl
- 31 (amide) compounds of the invention.

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- 2,2,4,4-Tetramethylchroman-6-carboxylic acid
- 33 (Compound O) is also converted to the methyl ester
- 34 (Compound T) which is then nitrated to yield

- 1 2,2,4,4-tetramethyl-8-nitrochroman-6-carboxylic acid
- 2 (Compound V), still another reagent within the scope
- of Formula 6. Moreover, in the example further
- 4 shown in Reaction Scheme 3,
- 5 2,2,4,4-tetramethylchroman- 6-carboxylic acid
- 6 (Compound O) is converted to the ethyl ester and
- 7 nitrated thereafter to yield ethyl
- 8 2,2,4,4-tetramethyl-8-nitrochroman-6-carboxylate
- 9 (Compound W). Still further, Compound O is reacted
- with ICl to yield 2,2,4,4-tetramethyl8-iodochroman-
- 11 6-carboxylic acid (Compound X).
- In accordance with the example shown in Reaction
- Scheme 4, 2-methylphenol is subjected to a series of
- 14 reactions in accordance with the teachings of United
- 15 States Patent No. 5,045,551 (incorporated herein by
- reference) to yield 2,2,4,4,8-pentamethylchroman
- (Compound Y). Compound Y is brominated with bromine
- in acetic acid to give 2,2,4,4,8-pentamethyl-6-
- bromochroman (Compound Z) which is reacted with
- \underline{t} -butyl lithium and thereafter with carbon dioxide
- to give 2,2,4,4,8-pentamethylchroman-6-carboxylic
- 22 acid (Compound A1).
- 23 Reaction Scheme 5 illustrates the synthesis of
- 4,4-dimethyl-8-bromochroman-6-carboxylic acid
- 25 (Compound B₁) by bromination of
- 26 4,4,-dimethyl-chroman-6-carboxylic acid which is
- 27 available in accordance with the teachings of United
- 28 States Patent No. 5,059,621, the specification of
- 29 which is incorporated herein by reference.
- 2,2,4,4,8-Pentamethylchroman-6-carboxylic acid
- 31 (Compound A₁) and 4,4,-dimethyl-8-bromochroman-
- 6-carboxylic acid (Compound B_1) serve as reagents,
- 33 either per se, or as the corresponding acid
- chlorides (or other "activated form), in accordance

```
with Formula 6 for the synthesis of the carbamoyl
    (amide) compounds of the present invention.
        Referring back now to the reaction between the
 3
    reagent of Formula 6 with an amine compound of
 4
    Formula 7 it is noted that the amine compounds are,
    generally speaking, available in accordance with the
 ĥ
    state-of-the-art. as described in the scientific and
 7
   patent literature. More specifically, the amine
 R
   compounds of Formula 7 can be prepared as described
 9
   in the scientific and patent literature, or from
10
   known compounds of the literature, by such chemical
11
   reactions or transformations which are within the
12
   skill of the practicing organic chemist.
13
   Scheme 6 illustrates examples for the preparation of
14
   amine compounds of Formula 7 (where Y is phenyl)
15
   from commercially available starting materials
16
   (Aldrich Chemical Company, or Research Plus, Inc.).
17
   The illustrated compounds of Formula 7 are used for
18
   the synthesis of several preferred compounds used in
19
   the methods of the invention.
20
```

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33

54 CO2C2H5 1) Na₂Cr₂O₇, HOAc, H₂SO₄, 90°C 1 2) SOCI₂ 2 3) EtOH/Py, CH₂Cl₂ 4) H₂, Pd/C NO2 H₂N 3 Compound C1 5 6 CO2C2H2 7 1) Na2Cr2O7, HOAc, H2SO4, 90°C 2) SOCl₂ 3) EtOH/Py, CH₂Cl₂ 8 NO₂ 4) H2. Pd/C H2N 10 Compound D1 11 12 CO2C2H5 13 1) Na2Cr2O7, HOAc, H2SO4, 90°C 2) SOCI₂ 14 3) EtOH/Py, CH₂Cl₂ NO₂ H₂N 4) H2. Pd/C 15 16 Compound E1 17 CO2H CO2CH3 1) SOCI₂ 18 2) MeOH/TEA/ CH2Cl2 19 H₂N NO₂ H₂N NO2 20 21 Compound F1 22 23 24 CO2H CO2C2H5 25 EDC, DMAP 26 **EtOH** H₂N 27 H₂N 28 Compound G1 29 30 1) SOCI2 2) CH3OH/Py CO2H 31 CO2CH3 3)NaN3/CH3CN 4)H2, Pd/C 32 33 H₂N 34 Reaction Scheme 6 Compound H1

- 55 Thus, in accordance with Reaction Scheme 6, 3-nitro-6-methyl-fluorobenzene (Aldrich) is 2 subjected to oxidation, conversion of the resulting carboxylic acid to an acid chloride and thereafter to an ethyl ester, followed by reduction of the 5 nitro group, to yield ethyl 6 2-fluoro-4-amino-benzoate (Compound C_1). 7 3-Nitro-6-methyl-bromobenzene (Aldrich) and 8 3-nitro-6-methyl-chlorobenzene (Aldrich) are 9 subjected to essentially to the same series of reactions to yield ethyl 2-bromo-4-amino-benzoate 11 (Compound D₁) and ethyl 2-chloro-4-amino-benzoate 12 (Compound E1), respectively. 2-Nitro-4-aminobenzoic acid (Research Plus) is converted to its methyl 14 ester ($Compound F_1$) through the corresponding acid 15 chloride. 2,3,5,6-Tetrafluoro-4-amino-benzoic acid 16 (Aldrich) is esterified by treatment with ethanol in 17 the presence of 1-(3-dimethylaminopropy1)-3ethylcarbodiimide hydrochloride (EDC) and 19 4-dimethylaminopyridine in CH2Cl2 to give ethyl 20 2,3,5,6-tetrafluoro-4-amino-benzoate (Compound G₁). 21 2,4,6-Trifluorobenzoic acid (Aldrich) is converted 22 to the methyl ester through the acid chloride, and 23 the 4-fluoro atom is displaced by reaction with 24 sodium azide, followed by hydrogenation, to yield 25 methyl 2,6-difluoro-4-amino benzoate (Compound H₁). 26 Compounds C_1 , D_1 , E_1 , F_1 , G_1 and H_1 serve as amine 27 reagents in accordance with Formula 7. examples of reagents in accordance with Formula 7 are nitro, fluoro, chloro, bromo and trifluoromethyl
- 28
- 29
- 30
- derivatives of amino substituted heteroaryl 31
- carboxylic acids, or their lower alkyl esters, such 32
- as ethyl 2-amino-4-chloropyridine 2-carboxylate, 33
- ethyl 5-amino-3-chloropyridine 5-carboxylate, and 34

```
3,4-dibromo-5-aminothiophene-2-carboxylic acid.
                                                     The
   latter examples quan be prepared by respective
2
   chlorination or bromination of
3
   2-aminopyridine-5-carboxylic acid or of its ester,
   3-aminopyridine-6-carboxylic acid or of its ester
5
   (described in WO 93/06086) and of
```

2-aminothiophene-5-carboxylic acid (described in 7

PCT/US92/06485). 8

The reactions between the compounds of Formula 6 and Formula 7 or between compounds of Formula 6a and 10 7a, described above, comprise the actual syntheses 11 of the carbamoyl (amide) compounds of the invention. 12 Numerous examples of this reaction are described in 13 detail in the experimental section below. 14 carbamoyl (amide) compounds of the invention can be 15 converted into thiocarbamoyl (thioamide) compounds 16 of the invention where with reference to Formula 1 Z 17 is S, by reacting the carbamoyl (amide) compound 18 with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-19 diphosphetane-2,4-disulfide (Lawesson's reagent). 20 This reaction is illustrated in Reaction Scheme 7 21 for two specific examples for the compounds used in 22

the methods of the invention.

24

23

25 26

27 28

29 30

31

32

33

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5
6
7
8
9
10
11
Compound I1
Compound 21
```

Compound 1 Compound 23

CO2Et

21

14

2

23

24

Reaction Scheme 7

In Reaction Scheme 7 one starting material ethyl 25 4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl-26 naphthalen-2-yl)carbamoyl]benzoate (Compound I1) is 27 obtained in accordance with the teachings of 28 <u>Kagechika et al.</u> J. Med Chem. 1988 31, 2182 - 2192. 29 The other starting material, ethyl 30 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra 31 methylnaphthalen-2-yl)carbamoyl]benzoate (Compound 32 1) is obtained in accordance with the present 33 invention. 34

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CO2C2H5 CO₂H Ethyl 4-amino-2-fluoro benzoate MOMO Compound C₁ Compound K1 Compound K CO2C2H5 K2CO3/acetone Thiophenol C7H15I BF3 O(C2H5)2 Compound ,CO₂C₂H₅ OC7H15 Compound L1

Reaction Scheme 8

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Reaction Scheme 9

NSDOCID: <WO___9724116A2_L>

33

Compound V

11 12 13 14 2) NaN₃ 15 16

Compound, 13

18

17

10

1

Reaction Scheme 10

Reaction Schemes 8, 9 and 10 disclose examples 20 for the preparation of carbamoyl (amide) compounds 21 of the invention, first by a coupling reaction of a 22 compound of Formula 6 with a compound of Formula 7, 23 followed by one or more reactions performed on the 24 carbamoyl (amide) compound that has been first 25 obtained directly in the coupling reaction. 26 as is shown in Reaction Scheme 8, 27 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-28 3-methoxymethoxynaphthalene-2-carboxylic acid 29 (Compound K) is coupled with ethyl 30 4-amino-2-fluorobenzoate (Compound C_1) in CH_2Cl_2 in 31 the presence of 1-(3-dimethylaminopropyl)-3ethylcarbodiimide hydrochloride (EDC) and 33 dimethylaminopyridine (DMAP) to give ethyl

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- 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra 1
- methyl-2'-methoxymethoxy-naphthalen-2
- 3'-y1)carbamoy1]benzoate (Compound K.). 3
- methoxymethyl protecting group is removed from
- Compound K, by treatment with thiophenol and 5
- borontrifluoride ethereate resulting in ethyl 6
- 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra 7
- methy1-2'-hydroxy-naphthalen-3'-y1)carbamoy1]-В
- benzoate (Compound 5). The hydroxy function of
- Compound 5 is converted into an \underline{n} -hexyl ether by 10
- treatment with hexyl iodide in the presence of mild 11
- base.
- In accordance with Reaction Scheme 9 13
- 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1-bromo-2-met 14
- hoxymethoxynaphthalene-3-carboxylic acid (Compound
- N) is coupled with methyl 4-amino-2,6-difluoro-16
- benzoate (Compound H₁) in CH₂Cl₂ solvent in the 17
- presence of ethylcarbodiimide hydrochloride (EDC) 18
- and DMAP to provide methyl 19
- 2,6-difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-20
- tetramethyl-1'-bromo-2'-methoxymethoxy-naphthalen-3' 21
- -yl)carbamoyl]benzoate (Compound M_i), from which the 22
- esterifying methyl group and the methoxymethyl 23
- protecting group are removed by treatment with base 24
- and acid, respectively to yield 25
- 2,6-difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-26
- tetramethyl-1'-bromo-2'-hydroxy-naphthalen-3'-yl)car 27
- bamoyl]benzoic acid (Compound 32). 28
- Reaction Scheme 10 discloses the example of 29
- converting 2,2,4,4-tetramethyl-8-nitrochroman-6-30
- carboxylic acid (Compound V) into the corresponding 31
- acid chloride by treatment with thionyl chloride, 32
- followed by coupling with ethyl 33
- 4-amino-2-fluorobenzoate (Compound C1) and

```
hydrogenation to yield ethyl
```

7 treatment with isoamyl nitrate and NaN3.

Reaction Scheme 11

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Reaction Scheme 11 illustrates the synthesis of 1 the primary amine compounds of Formula 6a from the 2 acid chlorides (X3 = C1) or other form of activated 3 acids of Formula 6 where the primary amine of Formula 6a is not available by a published 5 literature procedure. Thus, substantially in 6 accordance with the step of a Curtius rearrangement, 7 the acid chloride of Formula 6 is reacted with R sodium azide in acetone to yield the azide compound of Formula 9. The azide of Formula 9 is heated in a 10 polar high boiling solvent, such as t-butanol, to 11 provide the intermediate isocyanate of Formula 10, 12 which is hydrolyzed to yield a compound of Formula 13 6a. 14 15 16 CO2E CO2H 17 1) EtOH/H,SO4 18 2) BuLi/CO2 19 HO,C 20 Compound T₁ 21 Sugawara, S. Ishikawa, N. Kogyo Kaguku Zasshi 22 1970, 73, 972-979 23 24 CO2EI CO₂H 25 1) EtOH/H-SO. 26 2) BuLi/CO₂ 27 HO₂C 29 Michael Reuman et al Compound V₁ 30 J. Med. Chem. 1995, 38, 2531-2540 31

Reaction Scheme 12

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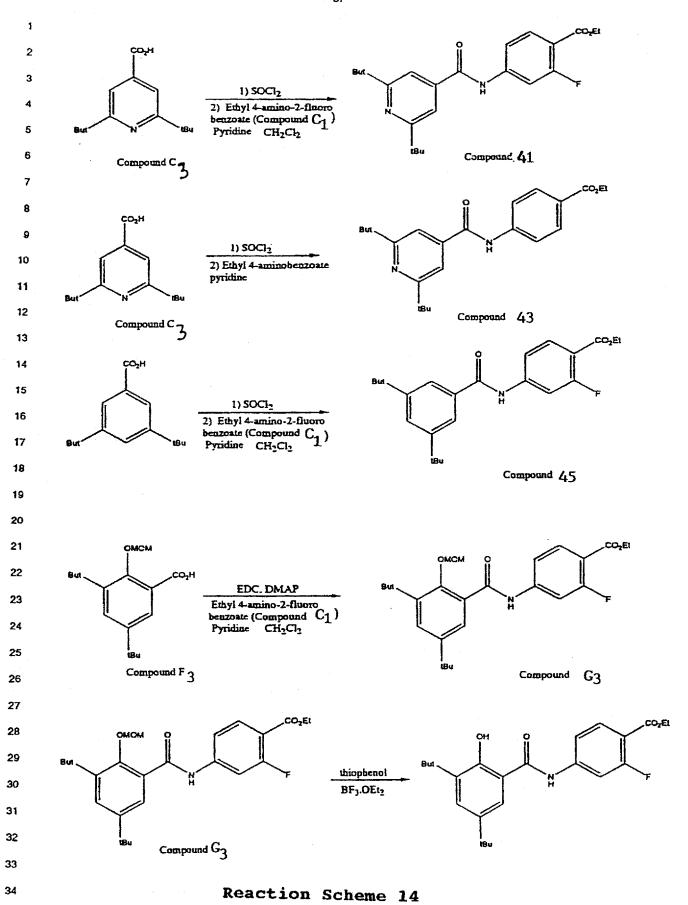
Reaction Scheme 12 illustrates examples for 1 preparing compounds of Formula 7a where such 2 compounds are not available commercially or by a 3 published literature procedure. Thus, by way of 4 example 2,5-difluoro-4-bromobenzoic acid (available 5 by the literature procedure of Sugawara et al. Kogyo 6 Kaguku Zasshi 1970, 73, 972-979) is first esterified 7 by treatment with ethyl alcohol and acid to yield 8 the corresponding ester, and thereafter is reacted 9 with butyl lithium followed by carbon dioxide to 10 give the monoester of 2,5-difluoro terephthalic acid 11 (Compound T₁). A similar sequence of reactions 12 performed on 2,3,5,6-difluoro-4-bromobenzoic acid 13 (available by the literature procedure of Reuman et 14 al. J. Med. Chem. 1995, 38, 2531-2540) yields the 15 monoester of 2,3,5,6-tetrafluoroterephthalic acid 16 (Compound V1). The just illustrated sequence of 17 reaction can be, generally speaking, utilized for 18 the synthesis of all compounds of Formula 7a with 19 such modification which will become readily apparent 20 to those skilled in the art, where such compounds 21 are not available by a known literature procedure. 22 Reaction Scheme 13 provides an example for the 23 preparation of 2,6-di-tert-butylisonicotinic acid 24 (Compound C3) which is a reagent in accordance with 25 Formula 8 for the preparation of several preferred 26 compounds of the present invention. 27 2,6-di-tert-butyl-4-methylpyridine (available 28 commercially from Aldrich Chemical Co.) is reacted 29 with N-bromosuccinimide and benzoyl peroxide to 30 provide 4-bromomethyl-2,6-di-tert-butylpyridine 31 Compound A, is reacted with base 32 (Compound A.). (sodium hydroxyde) to yield the coresponding 33 hydroxymethyl compound (Compound B3), which is 34

thereafter oxidized in a Jones oxidation reaction to give 2,6-di-tert-butylisonicotinic acid (Compound 2 C₃). 3 5 6 N₂OH NBS. (BzOh CCI 1.4-Dioxane reflux, lh Compound A 3 Compound Ba 10 11 12 ÇO₂H 13 14 Jone's/accrone 15 16 17 Compound C₃ 18 OH OMOM OH 19 But CH-OCH-CI 20 Br₂/HOAc Bu_sNBr 21 diisopropylethyl amine 22 23 24 Compound D3 Compound E₃ 25 26 MOMO 27 But. CO₂H 28 BuLi/CO-29 30 . Bu 31 Compound F.5 32 33 Reaction Scheme 13 34

```
66
        A further example of a compound which serves as
    a reagent for preparing the carbamoyl (or amide)
 2
    compounds of the present invention is provided in
 3
   Reaction Scheme 13. 2,4-Di-tert-butylphenol
    (Aldrich) is brominated in glacial acetic acid to
   yield 2-bromo-4,6-di-tert-butylphenol (Compound D3)
   which is thereafter reacted with methoxymethyl
   chloride (MOMCl)to give
   O-methoxymethyl-2-bromo-4,6-di-tert-butylphenol
Q
   (Compound E3). Compound E3 is treated with t-butyl
10
   lithium followed by carbon dioxide to yield
11
   O-methoxymethyl-3,5-di-tert-butylsalicylic acid
12
   (Compound F_3). Compound F_3 is a reagent which
13
   differs from the compounds generally encompassed by
14
   Formula 8 only in that the hydroxyl funtion of this
15
   compound is protected by the methoxymethyl (MOM)
          However, the methoxymethyl protecting group
17
   is removed after formation of the carbamoyl (amide)
18
   linkage, as exemplified in Reaction Scheme 14.
19
   Reaction of an aromatic bromo compound (such as
20
   Compound D_3) with t-butyl lithium followed by carbon
21
   dioxide is a preferred method for preparing several
22
   aromatic carboxylic acids in accordance with Formula
23
   8 and Formula 7a, described in the present
   application.
25
        The primary amine compounds of Formula 8a which
26
   are not available commercially or by a published
27
   literature procedure can be made from the acid
   chlorides (X_3 = Cl) or other form of activated acids
```

literature procedure can be made from the acid
chlorides (X₃ = Cl) or other form of activated acids
of Formula 8 substantially in accordance with the
steps of a Curtius rearrangement, in analogy to the
reaction steps described above in connection with
Reaction Scheme 11.

Section 2007 1 Section 2007 Section 2008



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Reaction Scheme 14 illustrates examples for the
 1
    formation of the carbamoyl (amide) compounds in
 2
    accordance with Formula 2, by reaction of a reagent
 3
    of Formula 8 with a reagent of Formula 7.
   2,6-di-tert-butylisonicotinic acid (Compound C3) is
 5
   reacted with thionyl chloride (SOCl,) to provide the
   intermediate acid chloride, which is then reacted
7
   with ethyl 2-fluoro-4-amino-benzoate (Compound C_1) in
   the presence of an acid acceptor (pyridine) to yield
   ethyl 2-fluoro-4-[(2'6'-di-tert-butylpyrid-4'-
10
   yl)carbamoyl]benzoate (Compound 41 ). As another
11
   example, 3,5-di-tert-butylbenzoic acid (available by
12
   the literature procedure of Kaqechika et al., J.
13
   Med. Chem. 1988, 31, 2182, incorporated herein by
14
   reference) is reacted with thionyl chloride,
15
   followed by ethyl 2-fluoro-4-amino-benzoate
16
   (Compound C<sub>1</sub>) to yield ethyl 2-fluoro-4-[(3',5'-di-
   tert-butylphenyl)carbamoyl]benzoate (Compound 45).
18
   As still another example, O-methoxymethyl-3,5-di-
19
   tert-butylsalicylic acid (Compound F,) is reacted with
20
   ethyl 2-fluoro-4-amino-benzoate (Compound C_1) in the
21
   presence of 4-dimethylaminopyridine (DMAP) catalyst
22
   and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
23
   hydrochloride (EDC) to give ethyl 2-fluoro-4-[(2'-
24
   methoxymethy1-3',5'-di-tert-butylphenyl)car-
25
   bamoyl]benzoate (Compound G_3). The methoxymethyl
26
   protecting group is removed from Compound G, by
27
   treatment with borontrifluoride ethereate and
28
   thiophenol to yield ethyl 2-fluoro-4-[(2'-hydroxy-
29
   3',5'-di-tert-butylphenyl)carbamoyl]benzoate
30
   (Compound 47).
31
        In yet another example shown in Reaction Scheme
32
   14, 2,6-di-tert-butylisonicotinic acid (Compound C_3)
33
   is reacted with thionyl chloride (SOCl2), the
34
```

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resulting intermediate acid chloride is reacted with
```

- 2 methyl 2,6-difluoro-4-amino benzoate (Compound H₁),
- 3 followed by saponification of the ester group, to
- 4 yield 2,6-difluoro-4-[(2',6'-di-tert-butylpyrid-
- 5 4'yl)carbamoyl]benzoic acid (Compound 50).
- 6 3,5-Di-tert-butylbenzoic acid is subjected to the
- 5 same sequence of reactions to provide
- 8 2,6-difluoro-4- [(3',5'-di-tert-butylphenyl)car-
- 9 bamoyl]benzoic acid (Compound 52).
- As yet another example, shown in Reaction Scheme
- 11 14, 2,6-di-tert-butylisonicotinic acid (Compound C₃)
- is reacted with thionyl chloride (SOCl2), followed by
- methyl 2-nitro-4-aminobenzoate (Compound F_1) and
- saponification of the ester function to give
- 2-nitro-4-[(2',6'-di-tert-butylpyrid-4'-yl)carbamoyl
- 16]benzoic acid (Compound 54).
- Numerous other reactions suitable for preparing
- 18 compounds of the invention, and for converting
- 19 compounds of Formula 1 and/or of Formula 2 into
- 20 still further compounds which can be used in the
- 21 methods of treatment of the present invention, and
- 22 also for preparing the reagents of Formula 6,
- 23 Formula 7, Formula 8, Formula 6a, Formula 7a and
- 24 Formula 8a will become readily apparent to those
- 25 skilled in the art in light of the present
- 26 disclosure. In this regard the following general
- 27 synthetic methodology, applicable for conversion of
- 28 the compounds of Formula 1 and/or of Formula 2 into
- 29 further homologs and/or derivatives, and also for
- opreparing the reagents of Formula 6, Formula 7, and
- 31 8, (as well as 6a, 7a and 8a) is noted.
- 32 Carboxylic acids are typically esterified by
- 33 refluxing the acid in a solution of the appropriate
- 34 alcohol in the presence of an acid catalyst such as

- 1 hydrogen chloride or thionyl chloride.
- 2 Alternatively, the carboxylic acid can be condensed
- 3 with the appropriate alcohol in the presence of
- 4 dicyclohexylcarbodiimide and dimethylaminopyridine.
- 5 The ester is recovered and purified by conventional
- 6 means. Acetals and ketals are readily made by the
- 7 method described in March, "Advanced Organic
- 8 Chemistry, " 2nd Edition, McGraw-Hill Book Company, p
- 9 810). Alcohols, aldehydes and ketones all may be
- o protected by forming respectively, ethers and
- esters, acetals or ketals by known methods such as
- those described in McOmie, Plenum Publishing Press,
- 13 1973 and Protecting Groups, Ed. Greene, John Wiley &
- 14 Sons, 1981.
- The acids and salts derived from compounds of
- 16 Formula 1 and Formula 2 are readily obtainable from
- 17 the corresponding esters. Basic saponification with
- an alkali metal base will provide the acid. For
- 19 example, an ester may be dissolved in a polar
- 20 solvent such as an alkanol, preferably under an
- inert atmosphere at room temperature, with about a
- 22 three molar excess of base, for example, potassium
- 23 or lithium hydroxide. The solution is stirred for
- 24 an extended period of time, between 15 and 20 hours,
- 25 cooled, acidified and the hydrolysate recovered by
- 26 conventional means.
- 27 The amide (in Formula 1 or 2 B is CONR, R₁₀) may
- 28 be formed by any appropriate amidation means known
- 29 in the art from the corresponding esters or
- 30 carboxylic acids. One way to prepare such compounds
- 31 is to convert an acid to an acid chloride and then
- 32 treat that compound with ammonium hydroxide or an
- 33 appropriate amine.
- 34 Alcohols are made by converting the

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corresponding acids to the acid chloride with
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- thionyl chloride or other means (J. March, "Advanced
- 3 Organic Chemistry", 2nd Edition, McGraw-Hill Book
- 4 Company), then reducing the acid chloride with
- s sodium borohydride (March, Ibid, pg. 1124), which
- 6 gives the corresponding alcohols. Alternatively,
- 7 esters may be reduced with lithium aluminum hydride
- at reduced temperatures. Alkylating these alcohols
- with appropriate alky halides under Williamson
- 10 reaction conditions (March, Ibid, pg. 357) gives the
- n corresponding ethers. These alcohols can be
- converted to esters by reacting them with
- 13 appropriate acids in the presence of acid catalysts
- or dicyclohexylcarbodiimide and
- 15 dimethylaminopyridine.
- Aldehydes can be prepared from the corresponding
- 17 primary alcohols using mild oxidizing agents such as
- 18 pyridinium dichromate in methylene chloride (Corey,
- 19 E. J., Schmidt, G., Tet. Lett., 399, 1979), or
- 20 dimethyl sulfoxide/oxalyl chloride in methylene
- chloride (Omura, K., Swern, D., <u>Tetrahedron</u>, 1978,
- 22 34, 1651).
- 23 Ketones can be prepared from an appropriate
- 24 aldehyde by treating the aldehyde with an alkyl
- 25 Grignard reagent or similar reagent followed by
- 26 oxidation.
- 27 Acetals or ketals can be prepared from the
- 28 corresponding aldehyde or ketone by the method
- 29 described in March, Ibid, p 810.

30

Specific Examples

- 2 Ethyl 4-Amino-2-fluorobenzoate (Compound C₁)
- To a mixture of 2-fluoro-4-nitrotoluene (1.0 g,
- 4 6.4 mmol, Aldrich) and $Na_2Cr_2O_7$ (2.74 g, 8.4 mmol) in
- 5 13.7 ml of HOAc was added slowly 6.83 ml of H_2SO_4 .
- 6 This mixture was slowly heated to 90 °C for 1 h to
- 7 give a greenish heterogeneous solution. The mixture
- was cooled to room temperature and diluted with
- ethyl acetate. The PH of the solution was adjusted
- 10 to 4 with NaOH (aq.). The mixture was extracted
- with more ethyl acetate. The organic layer was
- washed with NaHCO3 (sat.), then brine and dried over
- Na₂SO₄. After filtration, the solution was
- 14 concentrated to dryness which then was dissolved in
- 15 6 ml of SOCl2, and heated at 80 °C for 1 h. The
- excess of SOCl2 was removed under reduced pressure
- and the residue was dissolved in 5 ml of CH_2Cl_2 , 2 ml
- 18 of EtOH and 2 ml of pyridine. The mixture was
- 19 stirred at room temperature for 2 h and concentrated
- 20 to dryness. Ethyl 2-fluoro-4-nitrobenzoate was
- 21 obtained as a white solid after column
- 22 chromatography of the residue with ethyl
- 23 acetate/hexane (1/9). This solid was then dissolved
- 24 in 10 ml of ethyl acetate, and Pd/C (50 mg) was
- 25 added. Hydrogenation with a hydrogen balloon
- 26 converted ethyl 2-fluoro-4-nitrobenzoate into the
- 27 title compound.
- ²⁸ ¹H NMR δ 7.77 (t, J = 8.4 Hz, 1H), 6.41 (dd, J₁ =
- 29 8.6, $J_2 = 2.2 \text{ Hz}$, 1H), 6.33 (dd, $J_1 = 13.0$, $J_2 = 2.2$
- 30 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.3 (b, 2H), 1.37
- 31 (t, J = 7.1 Hz, 3H).
- Methyl 4-Amino-2,6-difluorobenzoate (Compound H₁)
- A solution of trifluorobenzoic acid (150 mg,
- 0.85 mmol, Aldrich) in 0.5 ml of SOCl2 was heated

- under reflux for 2h. The reaction mixture was
- 2 cooled to room temperature, and excess of SOCl, was
- 3 removed under reduced pressure. The residue was
- 4 dissolved in 1 ml of pyridine and 0.2 ml of
- methanol. After stirring at room temperature for 30
- 6 min, solvent was removed and the residue was
- 7 purified by column chromatography (ethyl
- 8 acetate/hexane 1/10) to give methyl trifluoro-
- p benzoate as a colorless oil. This oil was then
- odissolved in 1 ml of CH3CN, then a solution of NaN3
- 11 (100 mg, 1.54 mmol) in 0.5 ml of water was added.
- 12 The reaction mixture was refluxed for two days.
- 13 Salt was filtered and the remaining solution was
- 14 concentrated to an oil. This oil was then dissolved
- in 1 ml of methanol, followed by a catalytic amount
- of Pd/C (10%, w/w). The reaction mixture was
- hydrogenated under a hydrogen balloon for 12 h.
- 18 Catalyst was removed and the solution was
- 19 concentrated to an oil. After column chromatography
- 20 (ethyl acetate/hexane 1/3), the title product was
- obtained as colorless crystals.
- ²² ¹H NMR δ 6.17 (d, J = 10.44 Hz, 2H), 4.2 (b, 2H),
- 23 3.87 (s, 3H).
- 8-Bromo-2,2,4,4-tetramethyl-6-chromanoic acid
- 25 (Compound P)
- To a solution of 2,2,4,4-tetramethyl-6-chro-
- 27 manoic acid (200 mg, 0.85 mmol) in 0.5 ml of AcOH
- 28 was added Br_2 (0.07 ml, 1.28 mmol). The resulting
- 29 dark-orange solution was stirred at room temperature
- 30 for overnight. The excess bromine was removed under
- 31 reduced pressure. Then the solution was poured into
- 32 5 ml of water and extracted with ethyl acetate
- 33 (3x3ml). The combined ethyl acetate layers were
- 34 further washed with NaHCO3 (sat.), brine and dried

- over MgSO4. After concentration, the residue was
- 2 purified by column chromatography (silica gel, ethyl
- 3 acetate/hexane 1/3) to yield the desired product
- 4 (170 mg, as white solids.
- ⁵ ¹H NMR δ 8.11 (d, J = 2.2 Hz, 1H), 8.00 (d, J = 2.2
- 6 Hz, 1H), 1.90 (s, 2H), 1.43 (s, 6H), 1.39 (s, 6H).
- 7 8-Iodo-2,2,4,4-tetramethyl-6-chromanoic Acid
- 8 (Compound X)
- To a solution of 2,2,4,4-tetramethyl-6-chro-
- manoic acid (66 mg, 0.28 mmol) in 0.8 ml of AcOH was
- added ICl (0.07 ml, 1.4 mmol). The resulting
- 12 colored solution was stirred at room temperature for
- overnight. Following the same procedure as for the
- synthesis of 8-bromo-2,2,4,4-tetramethyl-6-
- 15 chromanoic acid (Compound P), the reaction gave the
- 16 title compound (107 mg) as white solids.
- ¹H NMR δ 8.35 (d, J = 2.2 Hz, 1H), 8.03 (d, J = 2.2
- 18 Hz, 1H), 1.87 (s, 2H), 1.43 (s, 6H), 1.38 (s, 6H).
- 2,2,4,4-Tetramethyl-8-trifluoromethylchroman-6-oic
- 20 acid (Compound S)
- A solution of 8-bromo-2,2,4,4-tetramethyl-6-
- 22 chromanoic acid (Compound R, 150 mg, 0.48 mmol) in 1
- 23 ml of SOCl₂ was refluxed for 2 h. After cooling to
- 24 room temperature, the excess of SOCl₂ was removed
- 25 under reduced pressure and the residue was dissolved
- 26 in 1 ml of pyridine and 0.2 ml of methanol. The
- 27 mixture was stirred at room temperature for 30 min.
- 28 Solvent was removed and the residue was passed
- 29 through a column (silica gel, ethyl acetate/hexane
- 30 1/10) to give the methyl 8-bromo-2,2,4,4-tetra-
- methylchromanoate (158 mg) as a colorless oil. To a
- 32 solution of this methyl ester in 3 ml of
- 33 N-methylpyrrolidone (NMP) was added NaCO₂CF₃ (502 mg,
- 34 3.7 mmol) and CuI (350 mg, 1.84 mmol). The

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- resulting mixture was heated to 175 °C (bath temp)
- 2 for 2 h. The resulting mixture was cooled to room
- 3 temperature and poured into ice-water. The product
- 4 was extracted into ethyl acetate (3x3ml). The
- 5 combined organic layers were dried and concentrated
- 6 to dryness. The crude material was purified by
- 7 column chromatography (ethyl acetate/chloroform
- 8 1/10) to give the title compound as a colorless oil
- 9 (120 mg). This was hydrolyzed under standard
- 10 conditions to give the title compound.
- ¹¹ ¹H NMR δ 8.21 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1
- 12 Hz, 1H), 1.92 (s, 2H), 1.41 (s, 12H).
- 13 Ethyl 8-Nitro-2,2,4,4-tetramethyl-6-chromanoate
- 14 (Compound W)
- Ethyl 2,2,4,4-tetramethyl-6-chromanoate (150 mg,
- 16 0.57 mmol) was slowly added to 0.3 ml of conc. H_2SO_4
- 17 at 0 °C. To this mixture was added very slowly 0.03
- 18 ml of HNO3. The reaction mixture was stirred at 0 °C
- 19 for 30 min and poured into ice-water. The product
- 20 was extracted into 5 ml of ethyl acetate, washed
- 21 with NaHCO3 (sat.), brine and dried over MgSO4.
- 22 After concentration, the product was purified by
- 23 column chromatography (ethyl acetate/hexane 1/10) to
- 24 yield 74 mg of light-yellow oil.
- ²⁵ ¹H NMR δ 8.24 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1
- $_{26}$ Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.95 (s, 2H),
- 27 1.43 (s, 6H), 1.42 (s, 6H), 1.40 (t, J = 7.1 Hz,
- 28 **3H)**.
- 29 2-0xo-4,4,8-trimethylchroman (Compound P₁)
- In a 500 ml of round bottom flask, NaH (1.66 g,
- 31 60% suspension in oil, 0.046 mol) was washed with
- 32 dry hexane. Then, dry THF (22 ml) was added
- 33 followed by \underline{o} -cresol (5 g, 0.046 mol) in 10 ml of
- 34 dry THF. The reaction mixture was stirred at 0 $^{\circ}\mathrm{C}$

- for 30 min followed by addition of 3,3-dimethyl
- 2 acryloyl chloride in 10 ml of THF. The resulting
- 3 white slurry was stirred at room temperature for 12
- 4 h, then slowly quenched with water. The mixture was
- 5 then extracted with ethyl acetate. The organic
- 6 layer was washed with brine, water and dried over
- 7 MgSO₄. After filtration and removal of the solvent,
- 8 a yellow oil was obtained (10.44 g). This oil was
- 9 then dissolved in 50 ml of dry CH₂Cl₂, and was
- canulated into a solution of AlCl₃ (10.8 g, 0.069
- mmol) in 10 ml of CH₂Cl₂. The reaction mixture was
- stirred at room temperature for 12 h. Then
- ice-water was carefully added and the organic layer
- was separated, and washed with NaHCO3 (sat), brine,
- water and finally dried over MgSO4. After removal of
- the drying agent and solvent, the residue was
- purified by column chromatography (silica gel, ethyl
- 18 acetate/hexane 1/9) to yield the title compound
- 19 (4.408 g) as an oil.
- ²⁰ ¹H NMR δ 7.1 (m, 3H), 2.62 (s, 2H), 2.33 (s, 3H),
- 21 1.36 (s, 6H).
- 22 2,4-Dimethyl-4-(2'-hydroxy-3'-methylphenyl)pentan-2-
- 23 ol (Compound R_1)
- To a solution of 2-oxo-4,4,8-trimethylchroman
- 25 (Compound P₁, 2.20 g, 11.5 mmol) in 40 ml of dry
- 26 ethyl ether was added methyl magnesium bromide
- 27 (12.67 ml, 38 mmol, 3 M solution in THF). The
- 28 reaction mixture was stirred at room temperature for
- 29 12 h, then quenched with NH₄Cl (sat.) until all
- mo precipitate dissolved. The mixture was extracted
- 31 with diethyl ether and the combined organic layers
- were separated and washed with brine, water and
- 33 dried over MgSO4. After filtration and removal of
- 34 the solvent, the title compound was obtained as a

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1 tan solid (2.215 g).
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- ² ¹H NMR δ 7.16 (d, J = 7.88 Hz, 1H), 7.00 (d, J = 6.72
- $_{3}$ Hz, $_{1H}$), 6.81 (t, $_{J}$ = 7.6 Hz, $_{1H}$), 5.89 (b, $_{1H}$),
- 4 2.21 (s, 3H), 2.17 (s, 2H), 1.48 (s, 6H), 1.10 (s,
- 5 6H).
- 6 2, 2, 4, 4, 8-Pentamethyl-6-bromochroman (Compound
- 7 Z) A solution of 2,4-dimethyl-4-(2'-hydroxy-3'-
- methylphenyl)pentan-2-ol (Compound R_1 , 2.215 g, 9.98
- mmol) in 30 ml of 15% of $\rm H_2SO_4$ was heated to 110 °C.
- 10 After cooling to room temperature, the reaction
- mixture was extracted with diethyl ether. The
- organic layer was washed with NaHCO3 (sat.), brine
- and water. After filtration and removal of solvent,
- 14 the residue was passed through a column (silica gel,
- pure hexane) to give the title compound as a clear
- oil (1.636 g). This oil was then dissolved in 1.5
- 17 ml of HOAc, then Br_2 (0.4113 ml, 7.98 mmol) was
- 18 added. The reaction mixture was stirred at room
- 19 temperature for 12 h. Solvent was removed under
- 20 reduced pressure and to the residue was added ethyl
- 21 acetate, and the resulting mixture was washed with
- 22 NaHCO3 (sat.), brine, water and dried over MgSO4.
- 23 After filtration and removal of solvent, the residue
- 24 was passed through a column (silica gel, pure
- 25 hexane) to give the title compound as a white solid
- 26 (2.227 g).
- ²⁷ ¹H NMR δ 7.21 (s, 1H), 7.06 (s, 1H), 2.14 (s, 3H),
- 28 1.79 (s, 2H), 1.32 (s, 6H), 1.31 (s, 6H).
- 29 2,2,4,4,8-Pentamethyl-6-chromanoic Acid (Compound A₁)
- To a solution of 2,2,4,4, 8-pentamethyl-6-bromo-
- 31 chroman (Compound Z) (1.2 g, 4.24 mmol) in 18 ml of
- 32 dry THF at -78 °C under argon gas was added slowly
- 33 5.48 ml of t-BuLi (1.7 M in hexane, 9.33 mmol). The
- 34 reaction mixture was stirred at -78 °C for 1 h. Then

- CO2 was bubbled through the solution for 1 h. After
- 2 removal of CO2 stream, the reaction mixture was
- 3 stirred for an additional hour at -78 °C. Then 10%
- 4 of HCl was added. After warming up to room
- temperature, the reaction mixture was extracted with
- 6 ethyl acetate. The organic layer was further washed
- 7 with brine and dried over Na₂SO₄. After
- 8 concentration, the residue was purified by column
- 9 chromatography (ethyl acetate/hexane 5/95) to yield
- the title compound as a white solid (774 mg).
- ¹¹ ¹H NMR δ 7.96 (s, 1H), 7.75 (s, 1H), 2.23 (s, 3H),
- 12 1.88 (s, 2H), 1.39 (s, 6H).
- 8-Bromo-4,4-dimethyl-6-chromanoic Acid (Compound B₁)
- Using the same procedure as for the synthesis of
- 8-bromo-2,2,4,4-tetramethylchromanoic acid (Compound
- P) but using 4,4-dimethylchromanoic acid (100 mg,
- 0.49 mmol), the title compound was obtained as a
- 18 White solid.
- ¹⁹ ¹H NMR δ 8.10 (d, J = 2.1 Hz, 1H), 7.98 (d, J = 2.1
- 20 Hz, 1H), 4.39 (t, J = 5.44 Hz, 2H), 1.89 (t, J = 5.4
- 21 Hz, 1H), 1.38 (s, 6H).
- 22 Ethyl 2-Amino-1-bromo-5,5,8,8-tetrahydro-5,5,8,8-
- 23 tetramethylnaphthalene-3-carboxylate (Compound D)
- To a solution of ethyl 5,6,7,8-tetrahydro-
- 5,5,8,8-tetramethyl-3-aminonaphthalene-2-carboxylate
- 26 (Compound C, 58 mg, 0.21 mmol) in 2 ml of HOAc was
- 27 added Br_2 (0.02 ml, 0.42 mmol). The orange solution
- 28 was stirred at room temperature for 2 days. The
- 29 excess Br₂ and HOAc were removed under reduced
- 30 pressure and the residue was passed through a column
- (silica gel, ethyl acetate/hexane 1/10) to yield the
- title compound as a light-orange oil (59 mg, 79.5%).
- ³³ ¹H NMR δ 7.90 (s, 1H), 6.41 (b, 2H), 4.36 (q, J = 7.2
- 34 Hz, 2H), 1.70 (m, 4H), 1.58 (s, 6H), 1.40 (t, J =

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1 7.2 Hz, 3H), 1.28 (s, 6H).
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- Ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl
- 3 -4-bromonaphthalene-2-carboxylate (Compound E)
- Ethyl 2-Amino-1-bromo-5,5,8,8-tetrahydro-
- 5 5,5,8,8-tetramethylnaphthalene-3-carboxylate
- 6 (Compound D, 59 mg, 0.17 mmol) was dissolved in 2 ml
- of EtOH at 0°C. To this solution was added 1ml of
- s trifluoroacetic acid and 1 ml of isoamylnitrite.
- 9 The reaction mixture was stirred at 0°C for 30 min
- then H_3PO_2 (0.325 ml, 3.14 mmol) was added. The
- n reaction mixture was allowed to warm to room
- temperature and stirred for 12 h. NaHCO3 (sat.) was
- added and the reaction mixture was extracted with
- ethyl acetate, dried over MgSO4, filtered and
- 15 concentrated to give an oil. The product was
- 16 purified by column chromatography (silica gel, ethyl
- acetate/hexane 1/10) to give the title compound as a
- 18 colorless oil.
- ¹⁹ ¹H NMR δ 8.02 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 2.0
- 20 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.71 (m, 4H),
- 21 1.56 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.31 (s,
- 22 6H).
- 23 Ethyl
- 24 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-fluoro-
- 25 <u>naphthalen-2-yl-carboxylate</u> (Compound G)
- In an ice bath, ethyl
- 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-aminonaphth
- 28 alene-2-carboxylate (Compound C, 150 mg, 0.55 mmol)
- 29 was added 0.24 ml of HBF, (48% solution in water),
- so followed by a solution of NaNO2 (81 mg, 1.16 mmol) in
- 31 1 ml of water. The slurry was left in a
- 32 refrigerator for 3 days. The reaction mixture was
- 33 washed successively with ethyl acetate until TLC
- 34 showed no UV visible spot at the baseline. The

- ethyl acetate layer was dried with MgSO, and the
- 2 solution was concentrated to an oil. The oil was
- 3 further dissolved in 1 ml of toluene and the mixture
- 4 was heated under reflux for 2 h. After the reaction
- 5 cooled to room temperature, solvent was evaporated
- 6 and the residue was passed through a column (silica
- 7 gel, ethyl acetate/hexane 1/10) to give the title
- s compound as an oil.
- 9 ¹H NMR δ 7.85 (d, J = 7.8 Hz, 1H), 7.04 (d, J = 12.3
- 10 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.69 (s, 4H),
- 11 1.38 (t, J = 7.1 Hz, 3H), 1.30 (s, 6H), 1.28 (s,
- 12 6H).
- 2-Bromo-3-hydroxy-5,5,8,8-tetrahydro-5,5,8,8-tetrame
- 14 thylnaphthalene (Compound I)
- Using the same procedure as for the synthesis of
- 8-bromo-2,2,4,4-tetramethyl-6-chromanoic acid
- (Compound P) but using 2-hydroxy-5,5,8,8-tetrahydro-
- 5,5,8,8-tetramethyltetralin (700 mg, 3.43 mmol) and
- 19 Br₂ (0.177 ml, 3.43 mmol) in 1.5 ml of HOAc, the
- 20 title compound was obtained as a white solid (747
- 21 mg).
- ²² ¹H NMR δ 7.36 (s, 1H), 6.96 (s, 2H), 5.32 (b, 1H),
- 23 1.66 (s, 4H), 1.25 (s, 12H).
- 24 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-methoxymet-
- 25 <u>hoxy-2-bromonaphthalene</u> (Compound J)
- To a solution of 2-bromo-3-hydroxy-5,5,8,8-tet-
- 27 rahydro-5,5,8,8-tetramethylnaphthalene (Compound I,
- 28 600 mg, 2.12 mmol) and catalytic amount of Bu₄NBr in
- 29 20 ml of dry CH₂Cl₂ at 0 °C was added
- 30 diisoproylethylamine (1.138 ml, 12.75 mmol),
- followed by methoxymethyl chloride (0.484 ml, 6.39
- 32 mmol). The reaction mixture was heated at 45 °C for
- 33 12 h. The reaction mixture was washed with 10% of
- 34 citric acid, then NaHCO3 (sat.), brine and dried over

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1 MgSO4. After filtration and removal of the solvent,
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- the residue was purified by column chromatography
- 3 (ethyl acetate/hexane 1/9) to yield the title
- 4 compound (722 mg) as a white solid.
- 5 ¹H NMR δ 7.43 (s, 1H), 7.06 (s, 1H), 5.21 (s, 2H),
- 6 3.54 (s, 3H), 1.66 (s, 4H), 1.26 (s, 6H), 1.25 (s,
- 7 6H).
- 8 3-Methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrah
- 9 ydronaphthalen-2-yl carboxylic acid (Compound K)
- Using the same procedure as for the synthesis of
- 11 2,2,4,4,8-pentamethyl-6-chromanoic acid (Compound A₁)
- but using 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-
- 3-methoxymethoxy-2-bromonaphthalene (Compound J, 722
- mg, 2.21 mmol) and 2.86 ml of t-BuLi (4.87 mmol, 1.7
- 15 M solution in hexane), the title compound was
- obtained as a white solid (143 mg).
- ¹H NMR δ 8.12 (s, 1H), 7.19 (s, 1H), 5.40 (s, 2H),
- 18 3.58 (s, 3H), 1.70 (s, 4H), 1.30 (s, 12H).
- 19 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-
- 20 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
- 21 <u>nzoate</u> (Compound 1)
- 22 To 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
- 23 2-naphthoic acid (46 mg, 0.2 mmol) was added 1 ml
- 24 thionyl chloride. This mixture was refluxed for 2
- 25 h. Excess thionyl chloride was removed under
- 26 reduced pressure and the residue was dissolved in 2
- 27 ml of CH2Cl2. To this solution was added ethyl
- 28 4-amino-2-fluorobenzoate ((Compound C1, 37 mg, 0.2)
- 20 mmol) followed by 0.5 ml of pyridine. The reaction
- 30 mixture was stirred at room temperature for 4 h and
- 31 was concentrated under reduced pressure. The
- 32 residue was purified by column chromatography (ethyl
- 33 acetate/hexane 1/10) to give the title compound as
- 34 white solids.

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- ¹ H NMR δ 8.06 (b, 1H), 7.93 (t, J = 8.4 Hz, 1H), 7.85
- 2 (d, J = 2.0 Hz, 1H), 7.78 (dd, $J_1 = 2.0 \text{ Hz}$, $J_2 = 12.9$
- 3 Hz, 1H), 7.55 (dd, $J_1 = 2.0 \text{ Hz}$, $J_2 = 8.2 \text{ Hz}$, 1H),
- 4 7.40 (d, J = 8.3 Hz, 1H), 7.32 (dd, $J_1 = 2.02 \text{ Hz}$, J_2
- 5 = 8.8 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 1.71 (s,
- $_{6}$ 4H), 1.40 (t, J = 7.2 Hz), 1.32 (s, 6H), 1.30 (s,
- 7 6H).
- Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-4'-
- 9 bromo-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbam
- 10 oyl]benzoate (Compound 3)
- Using the same procedure as for the synthesis of
- 12 ethyl 2-fluoro-4-[-5',6',7',8'-tetrahydro-
- 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
- 14 nzoate (Compound 1), but using
- 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-bromonaphth
- 16 alene-2-carboxylic acid (Compound F), the title
- 17 compound was obtained as a white solid.
- ¹⁸ ¹H NMR δ 8.30 (b, 1H), 7.92 (t, J = 8.4 Hz, 1H), 7.84
- 19 (d, J = 2.1 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.74
- 20 (dd, $J_1 = 2.1 \text{ Hz}$, $J_2 = 12.8 \text{ Hz}$, 1H), 7.35 (dd, $J_1 =$
- 21 2.0 Hz, $J_2 = 8.4$ Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H),
- 22 1.67 (m, 4H), 1.55 (s, 6H), 1.39 (t, J = 7.2 Hz,
- 23 3H), 1.31 (s, 6H).
- 24 Ethyl
- 25 2-Fluoro-4-[(3'-methoxymethoxy-5',6',7',8'-tet-
- 26 rahydro-5',
- 27 5',8',8'-tetramethylnaphthalen-2'-yl)car-
- 28 bamoyl]benzoate (Compound K,)
- Using the same procedure as for the synthesis of
- ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-
- 31 5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphth
- alen-2'-yl)carbamoyl]benzoate (Compound S_1), but
- using 3-methoxymethoxy-5,5,8,8-tetramethyl-
- 5,6,7,8-tetrahydronaphthalen-2-yl carboxylic acid

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1 (Compound K, 143 mg, 0.49 mmol) and
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- 2 4-amino-2-fluorobenzoate (Compound C1, 98.5 mg, 0.54
- mmol), the title compound was obtained as a white
- 4 solid.
- ⁵ ¹H NMR δ 10.1 (b, 1H), 8.20 (s, 1H), 7.93 (t, J = 8.8)
- 6 Hz, 1H), 7.83 (d, J = 13.4 Hz, 1H), 7.29 (d, J = 8.0
- 7 Hz, 1H), 5.41 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H),
- 8 3.59 (s, 3H), 1.70 (s, 4H), 1.31 (s, 12H), 1.26 (t,
- 9 J = 7.1 Hz, 3H).
- 10 Ethyl 2-Fluoro-4-[(3'-hydroxy-5',6',7',8'-
- tetrahydro-5',5',8', 8'-tetramethyl-2-
- 12 naphthalenyl)carbamoyl]benzoate (Compound 5)
- A solution of ethyl 2-fluoro-4-[(3'-methoxymet-
- 14 hoxy-5',6',7',8'-tetrahydro-5',
- 5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]
- benzoate (Compound K., 50.7 mg, 0.11 mmol) in 2 ml of
- 17 CH₂Cl₂ was added thiophenol (0.061 ml, 0.55 mmol).
- 18 The reaction mixture was stirred at 0 °C for 5 min,
- then BF₃.Et₂O (0.027 ml, 0.22 mmol) was added. The
- 20 reaction mixtrue was stirred at 0 °C for 2 h, then
- 21 NaHCO, (sat.) was added. The organic layer was
- 22 separated, and washed with brine, water and dried
- over MgSO. After filtration and removal of solvent,
- 24 the residue was passed through a column (silica gel,
- 25 ethyl acetate/hexane 1/3) to give the title compound
- 26 as white solid (44.2 mg).
- ³H NMR δ 8.61 (b, 1H), 7.94 (t, J = 8.42 Hz, 1H),
- 28 7.71 (dd, J = 10.8, 2.0 Hz, 1H), 7.53 (s, 1H), 7.35
- 29 (dd, J = 6.4, 2.0 Hz, 1H), 6.96 (s, 1H), 4.39 (q, J
- 30 = 7.1 Hz, 2H, 1.69 (s, 4H), 1.40 (t, J = 7.1 Hz,
- 3H), 1.29 (s, 6H), 1.27 (s, 6H).
- 32 Ethyl 2-Fluoro-4-[(4',4'-dimethyl-8'-bromochroman-
- 33 6'-yl)carbamoyl]benzoate (Compound 7)
- In a 10 ml of round bottom flask,

```
85
    4,4-dimethyl-8-bromo-6-chromanoic acid (Compound B,,
 1
    139 mg, 0.485 mmol) was added SOCl_2 (1 ml, large
 2
               The resulting solution was heated at 90 °C
    excess).
 3
    for 2 h and allowed to cool to room temperature.
    The excess of SOCl<sub>2</sub> was evaporated under reduced
 5
                The residue was dissolved in CH2Cl2 (3
    pressure.
 6
          Ethyl 4-amino-2-fluorobenzoate (Compound C1, 90
 7
    mq, 0.49 mmol) was added followed by pyridine (0.5
 8
    ml, large excess). The reaction mixture was stirred
 9
    for overnight and then concentrated to dryness.
10
    residue was purified by column chromatography with
11
    ethyl acetate/hexane (1/5) to yield the title
12
    compound as a white solid (190 mg).
13
    <sup>1</sup>H NMR \delta 7.95 (t, J = 8.31 Hz, 1H), 7.88 (b, 1H),
14
    7.83 (d, J = 2.2 \text{ Hz}, 1H), 7.80 (d, J = 2.2 \text{ Hz}, 1H),
15
    7.75 \text{ (dd, J = 12.89, 2.0 Hz, 1H), } 7.30 \text{ (dd, J = }
16
   8.55, 2.0 Hz, 1H), 4.37 (m, 5H), 1.89 (t, J = 5.49
17
   Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.39 (s, 6H).
   Ethyl 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromo-
19
   chroman-6'-yl)carbamoyl]benzoate (Compound 9)
20
        Using the same procedure as for ethyl
21
   2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
22
   rbamoyl]benzoate (Compound 7), but using
23
   2,2,4,4-tetramethyl-8-bromo-6-chromanoic acid
24
   (Compound P, 70 mg, 0.22 mmol) and ethyl
   4-amino-2-fluorobenzoate (Compound C_1, 38 mg, 0.22
26
   mmol), the title compound was obtained as a white
27
   solid (80 mg, 76%).
28
   <sup>1</sup>H NMR \delta 8.25 (b, 1H), 7.92 (t, J = 8.4 Hz, 1H),
   7.83 (s, 2H), 7.74 (dd, J_1 = 2.0, J_2 = 13.0 Hz, 1H),
```

30

7.34 (dd, $J_1 = 2.0$, $J_2 = 8.7$ Hz, 1H), 4.37 (q, J =31

7.1 Hz, 2H), 1.88 (s, 2H), 1.41 (s, 6H), 1.39 (t, J32

= 7.1 Hz, 3H), 1.37 (s, 6H).

Ethyl 34

3NSDOCID: <WO _9724116A2_l_>

```
2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluoromet
   hylchroman-6'-yl)carbamoyl] benzoate (Compound 11)
2
        Using the same procedure as for ethyl
3
   2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
4
   rbamoyl]benzoate (Compound 7), but using
5
   2,2,4,4-tetramethyl-8-trifluoromethyl-6-chromanoic
6
   acid (Compound S, 57 mg, 0.19 mmol) and ethyl
7
   4-amino-2-fluorobenzoate (Compound C,, 35 mg, 0.19
   mmol), the title compound was obtained as white
   solids.
10
   <sup>1</sup>H NMR \delta 8.06 (d, J = 2.2 Hz, 1H), 7.99 (b, 1H), 7.95
11
   (t, J = 8.55 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 7.76
12
   (dd, J = 12.8, 2.1 Hz, 1H), 7.33 (dd, J = 8.55, 1.9)
13
   Hz, 1H), 4.37 (q, J = 7.1 \text{ Hz}, 2H), 1.93 (s, 2H),
14
   1.41 (s, 12H), 1.40 (t, J = 7.2 \text{ Hz}, 3H). Ethyl
15
   2-Fluoro-4-[(2',2',4',4'-tetramethy1-8'-amino-
16
   chroman-6'-yl)carbamoyl]benzoate (Compound N<sub>1</sub>)
17
        Using 8-nitro-2, 2, 4,
18
   4-tetramethylchroman-6-carboxylic acid (Compound V)
19
   and following the same procedure as for the
20
   synthesis of ethyl 2-fluoro-4-[(4',4'-dimethyl-
21
   8'-bromochroman-6'-yl)carbamoyl]benzoate (Compound
22
   7), ethyl 2-fluoro-4-[2',2',4',4'-tetramethyl-
23
   8'-nitrochroman-6'-yl)]carbamoylbenzoate was
24
   obtained as a white solid. This compound (50 mg,
25
   0.12 mmol) was dissolved in 2 ml of methanol.
26
   catalytic amount of Pd/C was added to the solution
27
   and the solution was maintained under H2 atmosphere
28
   (hydrogen balloon) for overnight. The catalyst was
29
   removed by filtration and the solvent was evaporated
30
   to give the title compound as a white solid.
31
   <sup>1</sup>H NMR \delta 7.93 (t, J = 8.43 Hz, 1H), 7.90 (b, 1H),
32
   7.73 (dd, J = 12.9, 2.0 Hz, 1H), 7.29 (dd, J = 8.43,
33
   1.96 Hz, 1H), 7.23 (d, J = 2.14 Hz, 1H), 7.01 (d, J
34
```

- 1 = 2.2 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.88 (s,
- 2 2H), 1.39 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.37
- 3 (S, 6H).
- 4 Ethyl 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-
- 5 azidochroman-6'-yl)carbamoyl]benzoate (Compound 13)
- 6 To a solution of ethyl
- 7 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-aminochroman
- $6^{\circ}-6^{\circ}-y1$) carbamoyl] benzoate (Compound N₁, 32 mg, 0.077
- 9 mmol) in 3 ml of EtOH was added 0.5 ml of
- 10 trifluoroacetic acid (TFA) and 0.5 ml of
- isoamylnitrite at 0°C. The reaction was stirred for
- 2 h when a solution of NaN₃ (5 mg,) in 0.2 ml of
- water was added. The reaction mixture was allowed
- to warm to room temperature and stirred for
- overnight. The solvent was removed and the residue
- was purified by column chromatography (silica gel,
- ethyl acetate/ hexane 1/10) to give the title
- 18 compound as a colorless oil.
- ¹H NMR δ 8.0 (b, 1H), 7.94 (t, J = 7.8 Hz, 1H), 7.73
- 20 (d, J = 12.1 Hz, 1H), 7.64 (s, 1H), 7.31 (dd, J =
- 21 8.5, 2.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 4.37 (q,
- J = 7.1 Hz, 2H), 1.90 (s, 2H), 1.39 (t, J = 7.1 Hz,
- 23 3H), 1.45 (s, 6H), 1.40 (s, 6H).
- 24 Methyl
- 25 2,6-Difluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluor
- 26 omethylchroman-6'-yl)carbamoyl]benzoate (Compound
- 27 15)
- Using the same procedure as for ethyl
- 29 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
- 30 rbamoyl]benzoate (Compound 7), but using
- 31 2,2,4,4-tetramethyl-8-trifluoromethylchromanoic acid
- 32 (Compound S, 11.2 mg, 0.037 mmol) and methyl
- 4-amino-2,6-difluorobenzoate (Compound H_1 , 6.6 mg,
- 0.035 mmol), the title compound was obtained as

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white crystals.
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- ² ¹H NMR δ 8.21 (b, 1H), 8.05 (s, 1H), 7.82 (s, 1H),
- 3 7.36 (d, J = 10.20 Hz, 1H), 3.93 (s, 3H), 1.92 (s,
- 4 2H), 1.40 (s, 12H).
- 5 Ethyl 2-Fluoro-4-[(2', 2', 4',
- 6 4'-tetramethyl-8'-iodochroman-6'-yl)carbamoyl]benzoa
- 7 <u>te</u> (Compound 17)
- 8 Using the same procedure as for ethyl
- 9 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
- 10 rbamoyl]benzoate (Compound 7), but using
- 11 2,2,4,4-tetramethyl-8-iodochromanoic acid (Compound
- 12 X, 81 mg, 0.25 mmol) and ethyl 4-amino-2-
- 13 fluorobenzoate ((Compound C,, 55 mg, 0.30 mmol), the
- 14 title compound was obtained as a white solid.
- ¹H NMR δ 8.05 (b, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.94
- 16 (t, J = 8.4 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.75
- (dd, J = 12.88, 2.1 Hz, 1H), 7.33 (dd, J = 8.8, 2.1)
- 18 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.89 (s, 2H),
- 10 1.42 (s, 6H), 1.38 (s, 6H). Ethyl
- 20 2-Fluoro-4-[(2',2',4',4',8'-pentamethylchroman-
- 21 6'-yl)carbamoyl]benzoate (Compound 19)
- Using the same procedure as for ethyl
- 23 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
- 24 rbamoyl]benzoate (Compound 9), but using
- 25 2,2,4,4,8-pentamethyl-6-chromanoic acid (Compound
- A_1 , 92 mg, 0.37 mmol) and ethyl
- 27 4-amino-2-fluorobenzoate (Compound C,, 75 mg, 0.41
- 28 mmol), the title compound was obtained as a white
- 29 solid (100 mg).
- 30 ¹H NMR δ 8.31 (b, 1H), 7.90 (t, J = 8.24 Hz, 1H),
- 31 7.76 (dd, J = 14.29, 1.7 Hz, 1H), 7.74 (s, 1H), 7.43
- 32 (s, 1H), 7.35 (dd, J = 8.67, 1.7 Hz, 1H), 4.32 (q, J
- 33 = 7.1 Hz, 2H, 2.18 (s, 3H), 1.84 (s, 2H), 1.38 (t, 2H), 2.18 (s, 2H), 2.18 (t, 2H), 2.18 (t, 2H), 2.18 (s, 2H), 2.18 (t, 2H
- J = 7.1 Hz, 3H, 1.35 (s, 6H), 1.34 (s, 6H).

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PCT/US96/20511

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1 Ethyl
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2 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl-2

89

- 3 -naphthalenyl)thiocarbamoyl]benzoate (Compound 21)
- 4 To a solution of ethyl
- 5 4-[(5',6',7',8'-tetrahydro-5',5',8',
- 6 8'-tetramethylnaphthalen-2-yl)carbamoyl]benzoate
- 7 (Compound I_1 , 61 mg, 0.16 mmol) in 2 ml of anhydrous
- 8 benzene was added Lawesson's reagent (45 mg, 0.112
- 9 mmol). The resulting yellow solution was refluxed
- under N₂ for 2 h. The solvent was removed and the
- n residue was purified by column chromatography
- 12 (silica gel, ethyl acetate/hexane 1/5) to give the
- title compound as a yellow solid (55 mg, 87%).
- ¹⁴ ¹H NMR δ 9.04 (b, 1H), 8.11 (d, J = 8.70 Hz, 2H),
- 15 7.85 (b, 2H), 7.75 (b, 1H), 7.55 (dd, J = 8.2, 1.9
- 16 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 4.38 (q, J = 7.1
- 17 Hz, 2H), 1.71 (s, 4H), 1.40 (t, J = 7.1 Hz, 3H),
- 18 1.30 (s, 12H).
- 19 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-
- 20 5',5',8',8'-tetramethylnaphthalen-2'-yl)thiocarbamoy
- 21 <u>llbenzoate</u> (Compound 23)
- Using the same procedure as for the synthesis of
- 23 ethyl 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
- 24 tetramethyl-2-naphthalenyl)thiocarbamoyl]benzoate
- 25 (Compound 21) but using ethyl
- 26 2-fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
- 27 amethylnaphthalen-2'-yl)carbamoyl]benzoate (Compound
- 28 1, 167 mg, 0.42 mmol) in 8 ml of benzene and
- 29 Lawensson's reagent (220 mg, 0.544 mmol), the title
- 30 compound was obtained as a bright yellow solid
- 31 (127.5 mg).
- ³² ¹H NMR δ 9.30 (b, 1H), 8.05 (b, 1H), 7.95 (t, J =
- 33 8.37 Hz, 1H), 7.77 (d, J = 1.89 Hz, 1H), 7.53 (dd, J
- 34 = 8.24, 2.1 Hz, 1H), 7.49 (b, 1H), 7.35 (d, J = 8.24

3NSDOCID: <WO 9724116A2 L >

- 1 Hz, 1H), 4.33 (q, J = 7.1 Hz, 1H), 1.71. (s, 4H),
- 2 1.32 (s, 6H), 1.30 (s, 6H).
- 3 3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronap
- 4 hthalen-2-yl carboxylic acid (Compound L)
- To a solution of 2-bromo-3-methoxymethoxy-
- 5,5,8,8-tetrahydro-5,5,8,8-tetramethylnaphthalene
- 7 (Compound J, 722 mg, 2.2 mmol) in 10 ml of dry THF
- 8 at -78°C under argon was added slowly 2.86 ml of
- t-BuLi (1.7 M in hexane, 4.8 mmol). The reaction
- 10 mixture was stirred at -78°C for 1 h. Then CO₂ was
- bubbled through the solution for 1 h. After removal
- of CO₂ stream, the reaction mixture was stirred for
- an additional hour at -78°C. Then 10% of HCl was
- 14 added. After warming up to room temperature, the
- 15 reaction mixture was left overnight then extracted
- 16 with ethyl acetate. The organic layer was washed
- 17 with brine and dried over Na2SO4. After
- 18 concentration, the residue was purified by column
- o chromatography (ethyl acetate/hexane 1/3) to yield
- 20 the title compound as a white solid.
- 21 1H NMR d 7.85 (s, 1H), 6.93 (s, 1H), 1.68 (s, 4H),
- 22 1.28 (s, 12H).
- 23 <u>4-Bromo-3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrah</u>
- ydronaphthalen-2-yl carboxylic acid (Compound M)
- 25 3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
- naphthalen-2-yl acid (Compound L, 155 mg, 0.62 mmol)
- 27 was dissolved in 1 ml of HOAc. To this solution was
- added Br_2 (0.033 ml, 0.62 mmol). The reaction
- 29 mixture was left at room temperature for over night.
- 30 A stream of air was passed through the reaction
- 31 mixture to remove the unreacted Br₂. The remaining
- 32 solid was dissolved in small amount of THF and
- 33 purified by column chromatography (ethyl
- 34 acetate/hexane 1/1) to yield the desired product as

- Christian - Christian

- 1 a cream colored solid.
- ² ¹H NMR d 7.91 (s, 1H), 1.75 (m, 2H), 1.64 (m, 2H),
- 3 1,62 (s, 6H), 1.30 (s, 6H).
- 4 4-Bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8
- 5 -tetrahydronaphthalen-2-yl carboxylic acid (Compound
- 6 N)
- To a solution of 4-bromo-3-hydroxy-5,5,8,8-
- 8 tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl acid
- 9 (Compound M), 233 mg, 0.71 mmol) in 6 ml of CH_2Cl_2
- was added chloromethyl methyl ether (0.162 ml, 2.1
- mmol), diisopropylethyl amine (0.764 ml, 4.2 mmol)
- and a catalytic amount of tetrabutylammouimn
- 13 bromide. The reaction mixture was heated to 45 °C
- 14 for 2 h. The reaction mixture was concentrated and
- 15 the residue was purified by column chromatography
- 16 (ethyl acetate/hexane 1/9) to yield the
- methoxymethyl ester of the title compound as a white
- 18 solid (200 mg). This white solid was further
- 19 dissolved in 20 ml of EtOH. An aqueous solution of
- 20 NaOH (0.5 ml, 1M) was added. The reaction mixture
- 21 was stirred at room temperature for over night. The
- 22 EtOH was removed and the residue was added 2 ml of
- 23 ethyl acetate and 3 ml of water. This mixture was
- very slowly acidified with 10% HCl to PH = 7. The
- 25 ethyl acetate layer was separated and washed with
- 26 brine, dried over Na₂SO₄. After filtration of the
- 27 drying agent and removal of solvent, the reaction
- 28 yielded the title compound as a white solid (155
- ²⁹ mg). ¹H NMR d 7.99 (s, 1H), 5.20 (s, 2H), 3.66 (s,
- 30 3H), 1.74 (m, 2H), 1.67 (m, 2H), 1.60 (s, 6H), 1.32
- 31 (S, 6H).
- Ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-
- 33 5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphth
- 34 alen-2'-yl)carbamoyl]benzoate (Compound S₁)

```
To a solution of 4-bromo-3-methoxymethoxy-
 1
    5,5,8,8-tetramethy1-5,6,7,8-tetrahydronaphthalen-2-y
 2
    l acid (Compound N, 80 mg, 0.22 mmol) in 4 ml of
    CH,Cl, was added DMAP (60 mg, 0.26 mmol), ethyl
   2-fluoro-4-aminobenzoate (Compound C,, 43 mg, 0.24
   mmol) and EDC (50 mg, 0.26 mmol). The reaction
6
   mixture was stirred at room temperature for
7
   overnight and then concentrated to dryness.
8
   residue was purified by column chromatography (ethyl
9
   acetate/hexane 1/3) to yield the title compound as a
10
   clear oil (45 mg).
11
   <sup>1</sup>H NMR d 9.92 (b, 1H), 8.10 (s, 1H), 7.94 (t, J = 8.4
12
   Hz, 1H), 7.81 (dd, J = 12.9; 1.9 Hz, 1H), 7.35 (dd,
13
   J = 8.5; 1.8 Hz, 1H), 5.20 (s, 2H), 4.39 (q, J =
14
   7.1 Hz, 2H), 3.61 (s, 3H), 1.74 (m, 2H), 1.64 (m,
   2H), 1.60 (s, 6H), 1.40 (t, J = 7.1 \text{ Hz}, 3H), 1.34
16
   (s, 6H).
17
   <u>Methyl</u>
18
   2,6-Difluoro-4-[(3'-methoxymethoxy-4'-bromo-5',6',7'
19
   ,8'-tetrahydro-5',5',8',8'-tetramethylnaphtha-
20
   <u>len-2'-yl)carbamoyl]benzoate</u> (Compound M<sub>1</sub>)
21
        Using the same procedure as for the synthesis of
22
   compound ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-
23
   bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl
24
   naphthalen-2'-yl)carbamoyl]benzoate (Compound S1) but
25
   using 4-bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-
26
   5,6,7,8- tetrahydronaphthalen-2-yl acid (Compound N,
27
   80 mg, 0.22 mmol), DMAP (60 mg, 0.26 mmol), methyl
28
   2,6-difluoro-4-aminobenzoate (Compound H,, 52 mg,
29
   0.24 mmol) and EDC (50 mg, 0.26 mmol), the title
30
31
   compound was obtained as a clear oil.
   <sup>1</sup>H NMR d 10.01 (b, 1H), 8.11 (s, 1H), 7.42 (d, J =
32
   10.0 Hz, 2H), 5.2 (s, 2H), 3.95 (s, 3H), 3.63 (s,
33
   3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.35
```

```
1 (s, 6H).
```

- 2 4-Bromomethyl-2,6-di-t-butylpyridine (Compound A₃)
- To a mixture of 2,6-di-t-butyl-4-methylpyridine
- 4 (Aldrich, 2.0 g, 9.73 mmol) in 25 ml of dry CCl, was
- 5 added benzoyl peroxide (24 mg, 0.097 mmol) and NBS
- 6 (1.9 g, 10.7 mmol). The reaction mixture was
- 7 refluxed for 16 hours. After it cooled to room
- temperature, the solvent was removed in vacuo and
- 9 the residue was purified by column chromatography
- 10 (silica gel, hexane) to give an oil (1.957 g) which
- contained 82% of the desired product and 18% of the
- starting material. ¹H NMR δ 7.09 (s, 2H), 4.39 (s,
- 13 2H), 1.35 (s, 18H).
- 4-Hydroxymethyl-2,6-di-t-butylpyridine (Compound B₃)
- A heterogeneous solution of
- 4-bromomethyl-2,6-di-t-butylpyridine (Compound A3,
- 17 1.743 g, 82% purity) in 20 ml of 12% NaOH in water
- and 10 ml of 1,4-dioxane was refluxed for 12 hours.
- 19 The solution spontaneously separated into two layers
- 20 as it cooled to room temperature. The upper layer
- 21 was separated and ethyl acetate was added. This
- organic layer was then washed with brine, water and
- 23 dried over MgSO₄. The desired product was purified
- by column chromatography (ethyl acetate/hexane 1/9)
- to give a white solid. ¹H NMR δ 7.09 (s, 2H), 4.67
- ²⁶ (d, J = 4.4 Hz, 2H), 2.3 (b, 1H), 1.36 (s, 18H).
- 27 2,6-Di-t-butylisonicotinic acid (Compound C₃)
- Jone's reagent was added dropwise to a solution of
- 29 4-hydroxymethyl-2,6-di-t-butylpyridine (Compound B₃,
- 30 302 mg, 1.37 mmol) in 5 ml of acetone until the
- solution changed color from light yellow to orange
- 32 (55 drops of Jone's reagent were consumed). After 5
- minutes 2 ml of isopropanol were added to the
- reaction mixture, and a green precipitate of Cr3+

Liboration

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salt was formed.
                        The precipitate was removed by
   filtration and the solution was diluted with ethyl
2
   acetate, then washed with brine, water and dried
3
   over MqSO. After filtration, the solvent was
4
   removed to give the desired product as a white solid
5
    (227 mg). <sup>1</sup>H NMR \delta 7.71 (s, 2H), 1.34 (s, 18H).
6
   2-Bromo-4,6-di-t-butylphenol (Compound D,)
        To a solution of 2,4-di-t-butylphenol (Aldrich,
8
   2.0 g, 9.7 mmol) in 2 ml of HOAc was added Br, (0.5
9
   ml, 9.7 mmol). The reaction mixture was stirred at
10
   room temperature for 12 hours. Solvent was removed
11
   under reduced pressure and the residue was purified
12
   by column chromatography (ethyl acetate/hexane 1/20)
13
   to yield the desired product (2.54 g) as a white
14
            <sup>1</sup>H NMR \delta 7.33 (d, J = 2.3 Hz, 1H), 7.24 (d, J
15
   = 2.3 \text{ Hz}, 1\text{H}, 1.41 (s, 9\text{H}), 1.29 (s, 9\text{H}).
16
   O-Methoxymethyl-2-bromo-4,6-di-t-butylphenol
17
   (Compound E,)
18
        To a solution of 2-bromo-4,6-di-t-butylphenol
19
   (Compound D, 2.54 g, 8.88 mmol) and catalytic amount
20
   of Bu<sub>4</sub>NI in 20 ml of dry CH<sub>2</sub>Cl<sub>2</sub> at 0°C was added
21
   diisopropylethylamine (9.51 ml, 53 mmol), followed
22
   by methoxymethyl chloride (2.02 ml, 26.6 mmol).
23
   reaction mixture was heated to 45°C for 12 hours.
24
   The reaction mixture was then washed with 10% citric
25
   acid, then NaHCO3 (sat.), brine, and dried over
26
   MgSO. After filtration and removal of the solvent
27
   under reduced pressure, the residue was purified by
28
   column chromatography (pure hexane) to yield the
29
   title compound (2.79 g) as a colorless oil. <sup>1</sup>H NMR \delta
30
   7.40 (d, J = 2.44 \text{ Hz}, 1H), 7.30 (d, J = 2.4 \text{ Hz}, 1H),
31
32
   5.22 (s, 2H), 3.70 (s, 3H), 1.43 (s, 9H), 1.29 (s,
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34 O-Methoxymethyl-3',5'-di-t-butylsalicylic acid

33

9H).

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(Compound F<sub>3</sub>)
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- To a solution of O-methoxymethyl-2-bromo-4,6-
- di- \underline{t} -butylphenol (Compound E₃, 2.79 g, 8.5 mmol) in
- 4 30 ml of dry THF at -78°C under Ar was added 11 ml
- of t-BuLi (1.7 M in hexane, 18.7 mmol). This
- 6 mixture was stirred at -78°C for 1 hour. Then CO,
- 7 (g) was bubbled into the solution at -78°C for 1
- 8 hour. After removal of the CO₂ stream, the reaction
- 9 mixture was stirred for an additional hour at -78°C.
- 10 Then 10% of HCl was added and the mixture was
- allowed to warm to room temperature and extracted
- with ethyl acetate. The organic layer was washed
- with brine and dried over Na₂SO₄. After
- 14 concentration, the residue was purified by column
- chromatography (ethyl acetate/hexane 1/1) to yield
- the title compound as a white solid (492 mg). 1H NMR
- δ 7.75 (d, J = 2.81 Hz, 1H), 7.60 (d, J = 2.8 Hz,
- 18 1H), 5.07 (s, 2H), 3.62 (s, 3H), 1.33 (s, 9H), 1.26
- 19 (S, 9H).
- Ethyl 2-fluoro-4-[(2'6'-di-t-butylpyrid-4'-
- 21 <u>yl)carbamoyl]benzoate</u> (Compound 41)
- 22 A solution of 2,6-di-t-butylisonicotinic acid
- ²³ (Compound C_3 , 47.3 mg, 0.20 mmol) in 2 ml of $SOCl_2$
- was heated under reflux for 2 hours. Excess SOCl,
- 25 was removed in vacuo and the residue was dissolved
- in 2 ml of dry CH₂Cl₂, and ethyl
- 27 2-fluoro-4-aminobenzoate (Compound C1, 40.2 mg, 0.22
- 28 mmol) and pyridine (0.0835 ml, 0.69 mmol) were
- 29 added. The reaction mixture was stirred at room
- 30 temperature for 12 hours. Solvent was removed and
- 31 the residue was purified by column chromatography
- 32 (ethyl acetate/hexane 1/9) to yield the title
- 33 compound (71.2 mg) as white crystals. ^{1}H NMR δ 8.56
- 34 (b, 1H), 7.91 (t, J = 8.36 Hz, 1H), 7.53 (dd, J =

```
12.82, 2.0 Hz, 1H), 7.39 (dd, J = 8.7, 2.0 Hz, 1H),
    4.33 (q, J = 7.1 \text{ Hz}, 2H), 1.37 (t, J = 7.1 \text{ Hz}, 3H),
 2
    1.35 (s, 18H).
 3
    Ethyl 4-[(2',6'-di-t-butylpyrid-4'-yl)car-
 4
    bamoyl]benzoate (Compound 43)
        Using the same procedure as for the synthesis of
 6
   ethyl 2-fluoro-4-[(2'6'-di-t-butylpyrid-4'-
7
   yl)carbamoyl]benzoate (Compound 41) but using
   2,6-di-t-butylisonicotinic acid (Compound C3, 101 mg,
9
   0.43 mmol) and ethyl 4-aminobenzoate (78 mg, 0.47
10
   mmol), the title compound was obtained as a white
11
   solid (135 mg). <sup>1</sup>H NMR \delta 8.43 (b, 1H),, 8.02 (d, J =
12
   8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.48 (s, 2H),
13
   4.33 (q, J = 7.1 \text{ Hz}, 2H), 1.38 (t, J = 7.1 \text{ Hz}, 3H),
14
   1.35 (s, 18H).
15
        Ethyl
16
   2-Fluoro-4-[(3',5'-di-t-butylphenyl)carbamoyl]benzoa
17
   te (Compound 45)
18
        Using the same procedure as for the synthesis of
19
   ethyl 2-fluoro-4-[(2'6'-di-t-butylpyrid-4'-
20
   yl)carbamoyl]benzoate (Compound 41) but using
21
   3,5-di-t-butylbenzoic acid (60 mg, 0.26 mmol,
22
   available by literature procedure, see Kagechika et
   al. J. Med Chem. 1988 31, 2182 - 2192) and ethyl
24
   2-fluoro-4-aminobenzoate (Compound C1, 51.5 mg, 0.28
25
   mmol), the title compound was obtained as a white
26
   solid (66 mg). <sup>1</sup>H NMR \delta 8.21 (b, 1H), 7.93 (t, J =
27
   8.3 Hz, 1H), 7.79 (dd, J = 12.8, 2.0 Hz, 1H), 7.67
28
   (d, J = 1.8 Hz, 2H), 7.65 (t, J = 1.7 Hz, 1H), 7.35
29
   (dd, J = 8.7, 2.1 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H),
30
   1.39 (t, J = 7.2 \text{ Hz}, 3H), 1.36 (s, 18H).
31
        Ethyl
32
   2-Fluoro-4-[(2'-methoxymethyl-3',5'-di-t-butylphenyl
33
```

<u>)carbamoyl]benzoate</u> (Compound G,)

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```
To a mixture of O-methoxymethyl-3',5'-di-t-
  1
     butylsalicylic acid (Compound F3, 150 mg, 0.51 mmol),
 2
     4-dimethylaminopyridine (142 mg, 0.61 mmol) and
 3
    ethyl 2-fluoro-4-aminobenzoate (Compound C1, 102 mg,
    0.56 mmol) in 5 ml of dry CH2Cl2 was added 1-(3-di-
 5
    methylaminopropyl)-3-ethylcarbodiimide hydrochloride
 6
    (117 mg, 0.61 mmol). The reaction mixture was
 7
    stirred at room temperature for 12 hours. Solvent
 8
    was evaporated in vacuo and the residue was
 9
    dissolved in ethyl acetate, then washed with brine,
 10
    water and dried over MgSO4. After filtration,
 11
    solvent was removed and the residue was purified by
 12
    column chromatography (ethyl acetate/hexane 1/3) to
 13
    give the title compound (58 mg). <sup>1</sup>H NMR \delta 8.97 (b,
14
    1H), 7.94 (t, J = 8.37 \text{ Hz}, 1H), 7.78 (d, J = 2.7 \text{ Hz},
15
    1H), 7.61 (d, J = 13.0 \text{ Hz}, 1H), 7.56 (d, J = 2.6 \text{ Hz},
16
    1H), 7.35 (d, J = 8.7 \text{ Hz}, 1H), 5.00 (s, 2H), 3.53
17
    (s, 3H), 4.38 (q, J = 7.1 Hz, 2H), 1.47 (s, 9H),
18
    1.39 (t, J = 7.2 \text{ Hz}, 3H), 1.33 (s, 9H).
19
    Ethyl
20
    2-Fluoro-4-[(2'-hydroxy-3',5'-di-t-butylphenyl)carba
21
   moyl]benzoate (Compound 47)
22
        To a solution of ethyl 2-fluoro-4-[(2'-
23
   methoxymethy1-3',5'-di-t-butylphenyl)carbamoyl]benzo
24
   ate (Compound G3, 34 mg, 0.07 mmol) in 1 ml of THF
   were added 10 drops of HOAc.
26
                                   The reaction mixture
   was heated to reflux for 12 hours. Solvent was
27
   removed and ethyl acetate was added. The solution
28
   was washed with NaCHO3 (sat.), brine, water and dried
29
   over MgSO4. Solvent was removed in vacuo to give an
30
         The oil was allowed to be exposed to the
31
   atmosphere for 12 hours during which time crystals
32
             The crystals were collected and washed
   formed.
33
   several times with hexane to afford the title
34
```

```
compound as a white solid (13.5 mg). ^{1}\text{H} NMR \delta 10.73
 1
    (s, 1H), 7.98 (d, J = 2.56 Hz, 1H), 7.88 (b, 1H),
 2
    7.75 (t, J = 8.26 \text{ Hz}, 1H), 7.60 (d, J = 2.44 \text{ Hz},
    1H), 7.32 (dd, J = 12.3, 2.0 Hz, 1H), 7.02 (dd, J =
 4
    8.6, 2.0 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.39 (s,
 5
    9H), 1.37 (t, J = 7.2 \text{ Hz}, 3H), 1.5 (s, 9H).
 6
    2,6-Difluoro-4-[(2',6'-di-t-butylpyrid-4'yl)carbamoy
 7
    l|benzoic Acid (Compound 50)
 8
         To 2,6-di-\underline{t}-butylisonicotinic acid (Compound C_{3},
 9
    20 mg, 0.085 mmol) was added 1 ml of SOCl<sub>2</sub>.
10
    mixture was heated under reflux for 2 hours.
11
    cooling to room temperature, excess SOCl, was removed
12
    and the residue was dissolved in 2 ml of CH2Cl2.
13
    this solution was added methyl 2,6-difluoro-4-amino-
14
   benzoate (Compound H_1, 16 mg, 0.085 mmol) and
15
   triethylamine (0.015 ml, 0.1 mmol). The reaction
16
   mixture was kept at room temperature for 2 hours and
17
   then concentrated to dryness. The residue was
18
   purified by column chromatography with ethyl
19
   acetate/hexane (1/10) to yield the methyl ester of
20
   the title compound. This was saponified according
21
   to the general procedure (see below) to give the
22
   title compound as a colorless solid. ^{1}H NMR \delta 7.44
23
    (s, 2H), 7.40 (d, J = 11.8 Hz, 2H) 1.37 (s, 18H).
24
   2,6-Difluoro-4-[(3',5'-di-t-butylphenyl)car-bamoyl]b
25
26
   enzoic Acid (Compound 52)
        Using the same procedure as for the preparation
27
   of 2,6-difluoro-4-[(2',6'-di-t-butylpyrid-
28
   4'yl)carbamoyl]benzoic acid (Compound 50) but using
29
   3,5-di-\underline{t}-butylbenzoic acid (37 mg, 0.16 mmol) and
30
   methyl 2,6-difluoro-4-aminobenzoate (Compound \mathbf{H}_1, 29
31
   mg, 0.16 mmol), the title compound was obtained as
32
   colorless crystals. ^{1}H NMR \delta 7.92 (b, 1H) 7.60 (m,
```

3H), 7.42 (d, J = 10.0 Hz, 2H), 1.38 (s, 18H).

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34

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2-Nitro-4-[(2',6'-di-t-butylpyrid-4'-yl)carbamoyl]be
nzoic Acid (Compound 54)
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Using the same procedure as for the preparation

- of 2,6-difluoro-4-[(2',6'-di-t-butylpyrid-
- 5 4'yl)carbamoyl]benzoic acid (Compound 50) but using
- 6 2,6-di-t-butylisonicotinic acid (40 mg, 0.17 mmol)
- and methyl 2-nitro-4-aminobenzoate (Compound F1, 33
- mg, 0.17 mmol), the title compound was obtained as a
- 9 light yellow oil. ¹H NMR δ (acetone-d⁶) 10.25 (b,
- 10 lH), 8.32 (s, lH), 7.97 (d, J = 8.1 Hz, lH), 7.93
- 11 (b, 1H), 7.70 (s, 2H), 1.36 (s, 18H).
- 12 <u>Methyl 2-nitro-4-[(4'-bromo-5',6',7',8'-tetrahydro-</u>
- 13 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
- 14 <u>nzoate</u> (Compound 25)
- Using the same procedure as for the synthesis of Compound 1, but using Compound F and Compound F_1 , the
- desired product was obtained as a white solid.
- ¹⁸ ¹H NMR δ 9.24 (b, 1H), 9.23 (d, J = 1.8 Hz, 1H), 7.92
- 19 (dd, J = 8.4, 2.4, Hz, 1H), 7.87 (d, J = 2.1 Hz,
- 20 1H), 7.84 (d, 3 = 2.1 Hz, 1H), 7.80 (d, J = 8.7 Hz,
- 21 1H), 3.91 (s, 3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.58
- 22 (s, 3H), 1.33 (s, 3H).
- 23 General procedure for the syntheses of benzoic
- 24 acid derivatives by hydrolyzing the corresponding
- 25 methyl or ethyl esters.
- To a solution of ester (3.0 mmol) in 20 ml of
- 27 EtOH was added 5 ml of 1 N NaOH in water. The
- 28 reaction mixture was stirred at room temperature for
- 29 overnight and neutralized with 10% HCl to PH=5. The
- 30 alcohol was removed by evaporation and the aqueous
- layer was extracted with ethyl acetate (3x10ml).
- 32 The combined ethyl acetate layers were washed with
- 33 NaHCO3 (sat.), brine and dried over MgSO4. After
- 34 concentration, the desired acid was obtained which

- could be recrystallized in ethyl acetate or in
- 2 acetonitrile.
- 3 2-Fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
- 4 amethylnaphthalen-2'-yl)carbamoyl]benzoic Acid
- 5 (Compound 2)
- 6 ¹H NMR δ (acetone-D₆) 9.86 (b, 1H), 7.95 (m, 3H),
- 7 7.75 (dd, J = 7.9, 2.2 Hz, 1H), 7.62 (dd, J = 8.5,
- 8 1.6 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 1.73 (s, 4H),
- 1.32 (s, 6H), 1.30 (s, 6H).
- 10 <u>2-Fluoro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8</u>
- 11 /,8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
- 12 Acid (Compound 4)
- ¹³ ¹H NMR δ (acetone-D₆) 9.97 (b, 1H), 8.04 (d, J = 1.89)
- 14 Hz, 1H), 8.01 (d, J = 1.90 Hz, 1H), 7.95 (t, J =
- 15 8.55 Hz, 1H), 7.90 (dd, J = 12.28, 2.0 Hz, 1H), 7.59
- 16 (dd, J = 8.67, 1.50 Hz, 1H), 1.76 (m, 4H), 1.58 (s,
- 17 6H), 1.35 (s, 6H).
- 18 2-Fluoro-4-[(3'-hydroxy-5',6',7',8'-tetrahydro-5',5'
- 19 ,8',8'-tetramethylnaphthalen-2'-y1)carbamoy1]benzoic
- 20 Acid (Compound 6)
- ²¹ ¹H NMR (acetone-D₆) δ 11.3 (b, 1H), 10.2 (b, 1H),
- 22 7.94 (m. 2H), 7.85 (dd, J = 11.4, 1.95 Hz, 1H), 7.53
- 23 (dd, J = 6.59, 2.08 Hz, 1H), 6.94 (s, 1H), 2.85 (b,
- 24 1H), 1.70 (s, 4H), 1.29 (s, 6H), 1.28 (s, 12H).
- 25 2-Fluoro-4-[(8'-bromo-4',4'-dimethylchroman-6'-yl)ca
- 26 <u>rbamoyl]benzoic Acid</u> (Compound 8)
- ²⁷ ¹H NMR (acetone-d₆) δ 9.87 (b, 1H), 8.04 (d, J = 2.1
- 28 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.94 (t, J = 8.66
- 29 Hz, 1H), 7.91 (dd, J = 13.8, 2.0 Hz, 1H), 7.57 (dd,
- 30 J = 8.6, 2.0 Hz, 1H), 4.37 (t, J = 5.44 Hz, 2H),
- 31 1.92 (t, J = 5.44 Hz, 2H), 1.40 (s, 6H).
- 32 2-Fluoro-4-[(2',2',4',4'-tetramethy1-8'-bromochroman
- 33 6'-yl)carbamoyl]benzoic Acid (Compound 10)
- ³⁴ ¹H NMR δ (acetone-d₆) 9.87 (b, 1H), 8.06 (d, J = 2.2

- 1 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.94 (t, J = 8.54
- 2 Hz, 1H), 7.91 (dd, J = 14.0, 2.0 Hz, 1H), 7.59 (dd,
- 3 J = 8.5, 2.3 Hz, 1H), 1.96 (s, 2H), 1.42 (s, 6H),
- 4 1.41 (s, 6H).
- 5 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluoro-
- 6 methylchroman-6'-yl)carbamoyl] benzoic Acid
- 7 (Compound 12)
- 8 1 H NMR (acetone-d₆) δ 10.02 (b, 1H), 8.31 (s, 1H),
- 9 8.09 (s, 1H), 7.92 (m, 2H), 7.56 (d, J = 7.69 Hz,
- 10 1H), 2.00 (s, 2H), 1.44 (s, 6H), 1.41 (s, 6H).
- 11 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-azidochroman
- 12 6'-yl)carbamoyl]benzoic Acid (Compound 14)
- ¹³ ¹H NMR δ 8.03 (t, J = 8.4 Hz, 1H), 7.87 (b, 1H), 7.79
- 14 (dd, J = 13, 2.0 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H),
- 15 7.32 (dd, J = 8.66, 1.9 Hz, 1H), 7.22 (d, J = 2.1
- 16 Hz, 1H), 1.91 (s, 2H), 1.45 (s, 6H), 1.41 (s, 6H).
- 17 2, 6-Difluoro-4-[(2',2',4',4'-tetramethyl-8'-
- 18 trifluoromethylchroman-6'-yl)carbamoyl]benzoic acid
 - 19 (Compound 16)
 - ¹H NMR (acetone-d₆) δ 8.30 (d, J = 2.3 Hz, 1H), 8.06
 - 21 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 10.32 Hz, 2H),
 - 22 1.954 (s, 2H), 1.44 (s, 6H), 1.41 (s, 6H).
 - 23 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-iodochroman-
 - 24 6'-yl)carbamoyl]benzoic Acid (Compound 18)
 - 25 ¹H NMR δ (acetone-d₆) 10.0 (b, 1H), 8.24 (s, 1H),
 - 26 8.07 (s, 1H), 7.94 (m, 2H), 7.57 (d, J = 8.67 Hz,
 - 27 1H), 1.95 (s, 2H), 1.41 (s, 12H).
 - 28 2-Fluoro-4-[(2',2',4',4',8'-pentamethylchroman-6'-yl
 - 29 <u>)carbamoyl]benzoic Acid</u> (Compound 20) ¹H NMR δ
 - 30 (acetone- d_6) 9.77 (b, 1H), 7.90 (m, 3H), 7.65 (d, J =
 - 31 2.0 Hz, 1H), 7.56 (dd, J = 8.61, 2.0 Hz, 1H), 2.19
 - 32 (s, 3H), 1.90 (s, 2H), 1.38 (s, 6H), 1.37 (s, 6H).
 - 33 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylna
 - 34 phthalen-2'-yl)thiocarbamoyl]benzoic Acid (Compound

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1 22)
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- ² ¹H NMR δ 9.08 (b, 1H), 8.17 (d, J = 8.61, 2H), 7.95
- $_3$ (b, 2H), 7.77 (b, 1H), 7.57 (dd, J = 8.1, 2.1 Hz,
- 4 1H), 7.37 (d, J = 8.2 Hz, 1H), 1.72 (s, 4H), 1.32
- 5 (s, 6H), 1.31 (s, 6H).
- 6 2-Fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
- 7 amethylnaphthalen-2'-yl)thiocarbamoyl]benzoic Acid
- 8 (Compound 24)
- 9 ¹H NMR δ (acetone-d₆) 11.1 (b, 1H), 8.27 (b, J = 13.2
- 10 Hz, 1H), 8.02 (t, J = 8.3 Hz, 1H), 7.89 (s, 1H),
- 7.86 (d, J = 10.0 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H),
- 7.41 (d, J = 8.37 Hz, IH), 1.72 (s, 4H), 1.30 (s,
- 13 12H).
- 14 2-Fluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tetrahy
- dro-5',5', 8',8'-tetramethylnaphthalen-2'-
- 16 <u>yl)carbamoyl]benzoic Acid</u> (Compound 30)
- A solution of ethyl 2-fluoro-4-[(3'-
- methoxymet-hoxy-4'-bromo-5',6',7',8'-tetrahydro-5',5
- ',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoa
- te (Compound S_1 , 45 mg, 0.084 mmol) in 1 ml of EtOH
- 21 was added 1 ml of aqueous solution of NaOH (1M).
- 22 The reaction mixture was stirred at room temperature
- 23 for overnight and acidified to PH = 1 with 10% HCl.
- 24 EtOH was removed and ethyl acetate and more water
- 25 were added to the solution. The organic layer was
- 26 separated and washed with NaHCO3, brine and dried
- over MgSO4. After filtration and concentration, the
- 28 reaction yielded 2-fluoro-4-[(3'-methoxymethoxy-
- 29 4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramet
- 30 hylnaphthalen-2'-yl)carbamoyl]benzoic acid as a
- white solid. The methoxymethyl group was removed by
- 32 dissolving the white solid in 2 ml of MeOH and 3
- 33 drops of HCl (con.). After stirring for overnight,
- 34 the reaction mixture was concentrated to dryness.

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- 1 The residue was partitioned between ethyl acetate
- and water. The organic layer was separated, washed
- 3 with NaHCO3, brine and dried over MgSO4. After
- 4 filtration and concentration, the residual solid was
- 5 purified in a mini (pipette) column with ethyl
- 6 acetate /hexane (1/1) to give the title compound as
- 7 a white solid (5.0 mg).
- 8 1H NMR d (acetone-d6) 10.19 (b, 1H), 8.01 (s, 1H),
- 9 7.96 (t, J = 8.6 Hz, 1H), 7.76 (dd, J = 11.2; 2.0
- 10 Hz, 1H), 7.54 (dd, J = 8.8; 2.0 Hz, 1H), 1.75 (m,
- 11 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.32 (s, 6H).
- 12 2,6-Difluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tet
- rahydro-5', 5',8',8'-tetramethylnaphthalen-2'-
- 14 <u>yl)carbamoyl]benzoic Acid</u> (Compound 32)
- Using the same procedure as for the synthesis of
- 16 2-fluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tetrahy
- -dro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamo
- 18 yl]benzoic acid (Compound 30) the title compound was
- obtained as a white solid.
- 20 ¹H NMR d(acetone- d^6) 10.23 (b, 1H), 8.01 (s, 1H),
- 21 7.52 (d, J = 10.2 Hz, 2H), 4.8 (b, 1H), 1.75 (m,
- 22 2H), 1.65 (m, 2H), 1.60 (s, 6H), 1.31 (s, 6H).
- 23 2,6-Difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
- 24 <u>tetramethylnaphthalen-2'-yl)carbamoyl]benzoic Acid</u>
- 25 (Compound 34)
- To 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
- 27 2-naphthoic acid (43 mg, 0.19 mmol) was added 1 ml
- 28 of thionyl chloride. This mixture was refluxed for
- 29 2 h. Excess thionyl chloride was removed under
- meduced pressure and the residue was dissolved in 2
- 31 ml of CH2Cl2. To this solution was added methyl
- 4-amino-2,6-difluorobenzoate (Compound H₁, 7 mg, 0.2
- mmol) followed by 0.5 ml of pyridine. The reaction
- 34 mixture was stirred at room temperature for 4 h and

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- was concentrated under reduced pressure. residue was purified by column chromatography (ethyl 2 acetate/hexane 1/5) to give the methyl ester of the 3 desired product as a colorless oil. 4 ¹H NMR d 8.11 (d, J = 1.9 Hz, 1H), 8.05 (b, 1H), 7.86 5 (dd, J = 6.2, 2.2 Hz, 1H), 7.41 (m, 3H), 3.93 (s,3H), 1.69 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H). This 7 colorless oil was hydrolyzed to the desired product 8 with NaOH/H,O/EtOH according to the general procedure. 10 ¹H NMR d (acetone- d^6) 9.74 (b, 1H), 7.95 (s, 1H), 11 7.70 (d, J = 6.8 Hz, 1H), 7.43 (d, J = 8.4 Hz, 3H), 12 1.71 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H).13 2-Nitro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8' 14 ,8',-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic 15 acid (Compound 26) 16 ¹H NMR δ (acetone-d⁶): 10.16 (b, 1H), 8.42 (d, J = 17 2.0 Hz, 1H), 8.09 (dd, J = 8.6; 2.1 Hz, 1H), 8.0618 (d, J = 2.2 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.9319 (d, J = 8.6 Hz, 1H), 1.75 (m, 2H), 1.65 (m, 2H),20 1.57 (s, 3H), 1.34 (s, 3H). 21 2-Fluoro-4-[(2',6'-di-t-butylpyrid-4'-yl)carbamoyl]b 22 enzoic Acid (Compound 42) 23 ¹H NMR δ (CD₃OD) 7.92 (t, J = 8.36 Hz, 1H), 7.82 24 (dd, J = 12.82, 2.0 Hz, 1H), 7.63 (s, 2H), 7.55 (dd,25 J = 8.7, 2.1 Hz, 1H), 1.39 (s, 18H).26 4-[(2',6'-Di-t-butylpyrid-4'-yl)carbamoyl]benzoic 27 acid (Compound 44) 28 ¹H NMR δ (CD₃OD) 8.02 (d, J = 8.85 Hz, 2H), 7.85 29 (d, J = 8.85 Hz, 2H), 7.63 (s, 2H), 1.40 (s, 18H).30 2-Fluoro-4-[(3',5'-di-t-butyl)phenylcarbamoyl]benzoi 31 c acid (Compound 46) 32
- ¹H NMR δ (CD₃OD) 7.92 (t, J = 8.3 Hz, 1H), 7.80 (dd, J = 12.8, 2.0 Hz, 1H), 7.79 (d, J = 1.8 Hz,

rC1/U390/20311

- 1 2H), 7.69 (t, J = 1.7 Hz, 1H), 7.57 (dd, J = 8.7,
- 2 2.1 Hz, 1H), 1.37 (s, 18H).
- 3 2-Fluoro-4-[(2'-hydroxy-3',5'-di-t-butyl)phenylcarba
- 4 movl]benzoic acid (Compound 48)
- ¹H NMR δ (acetone- d_6) 12.3 (b, 1H), 10.07 (b,
- 6 1H), 7.98 (t, J = 8.48 Hz, 1H), 7.80 (m, 2H), 7.58
- 7 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 8.8, 2.0 Hz, 1H),
- 8 1.44 (s, 9H), 1.31 (s, 9H).

WHAT IS CLAIMED IS:

- 2 1. A process of administering to a mammal a
- 3 retinoid campound which binds specifically or
- 4 selectively to a RAR_{α} retinoid receptors in
- 5 preference over RARB and RARr retinoid receptors, for
- 6 the purpose of treating or preventing a disease or
- 7 condition which is responsive to treatment by RAR,
- s specific or selective retinoid agonists.
- A process in accordance with Claim 1 where
- the RAR_{α} specific or selective retinoid compound
- binds approximately 500 times stronger to RAR,
- 12 retinoid receptors than to RAR_B and RAR_r retinoid
- 13 receptors.

- 3. A process in accordance with Claim 1 where
- the RAR_{α} specific or selective retinoid compound is
- administered to a mammal for the treatment or
- 17 prevention of the disease or condition selected from
- 18 acute monocytic leukemia, cervical carcinoma,
- myeloma, ovarian carcinomas, head and neck
- 20 carcinomas, proliferative vitreoretinopathy (PVR)
- and age related macular degeneration (AMD).
- 22 4. A process in accordance with Claim 3 where
- 23 the RAR_{α} specific or selective retinoid compound is
- 24 administered in a dose of approximately 0.5 to 5 mg
- 25 per kg body weight per day.
- 5. A process in accordance with Claim 1 where
- 27 the RAR_{α} specific or selective retinoid compound is
- 28 administered to a mammal for the treatment or
- 29 prevention of the disease or condition selected from
- 30 actinic keratoses, arsenic keratoses, inflammatory
- and non-inflammatory acne, psoriasis, ichthyoses,
- 32 eczema, atopic dermatitis, Darriers disease, lichen
- 33 planus, glucocorticoid damage, topical microbial
- 34 infection, skin pigmentation, age and photo damage

to the skin, premalignant and malignant

2 hyperproliferative diseases, Kaposi's sarcoma,

diseases of the eye, proliferative vitreoretinopathy

4 (PVR), retinal detachment, dry eye and other

5 corneopathies, cardiovascular diseases,

6 dyslipidemias, prevention of post-angioplasty

7 restenosis, diseases associated with human papilloma

8 virus (HPV), inflammatory diseases,

neurodegenerative diseases, improper pituitary

10 function, insufficient hair growth, diseases

associated with the immune system, and wound

12 healing.

6. A process in accordance with Claim 1 where the RAR $_{\alpha}$ specific or selective retnoid compound has the formula (i) or the formula (ii)

17 18

19

20

21

22

23

24

16

$$(R_3)_0$$
 $(W_1)_p$
 $(R_2)_m$
 $(W_2)_m$

(R₂)m

L — Y(W₂)r — B

(W₃)p

25 26

27

28

34

formula (i) formula (ii)

where X_1 is 0 or X_1 is $[C(R_1)_2]_n$ where n is an integer between 0 and 2;

R₁ is independently H or alkyl of 1 to 6 carbons:

R2 is independently hydrogen, or lower alkyl of

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```
1 to 6 carbons;
        R, is hydrogen, lower alkyl of 1 to 6 carbons or
2
3
   F;
        m is an integer having the value of 0 - 5;
4
        o is an integer having the value of 0 - 4;
        p is an integer having the value of 0 - 2;
        r is an integer having the value 0 - 2;
7
        X, is N or CH;
        Y is a phenyl or naphthyl group, or heteroaryl
9
   selected from a group consisting of pyridyl,
10
   thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
11
   thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said
12
   phenyl, naphthyl and heteroaryl groups being
13
   optionally substituted with one or two R, groups;
14
        W<sub>1</sub> is a substituent selected independently from
15
   the group consisting of F, Br, Cl, I, fluoro
16
   substituted C1-6 alkyl, NO2, and OH, with the provisos
17
   that:
18
             when the compound is in accordance with
19
   formula (i) and Z is 0 then the sum of p and r is at
20
   least 1 and W<sub>1</sub> is not a fluoro group in the 3
21
   position of a tetrahydronaphthalene ring;
22
        (ii) when the compound is in accordance with
23
   formula (i) and r is zero and p is 1 and W, is OH
24
   then the OH group is positioned \alpha to the L group;
25
        W<sub>2</sub> is a substituent selected independently from
26
   the group consisting of F, Br, Cl, I, fluoro
27
   substituted C_{1-6} alkyl, NO_2, and OH;
28
        W, is a substituent selected independently from
29
   the group consisting of F, Br, Cl, I, C1-6alkyl,
30
   fluoro substituted C1-6 alkyl, NO2, and OH with the
31
   proviso that when the compound is in accordance with
32
   Formula 2 and X_2 is CH and r is 0 then p is not 0 and
33
   at least one W, group is not alkyl;
34
```

- L is -(C=Z)-NH- or -NH-(C=Z)- Z is 0 or S,
- 2 and
- B is COOH or a pharmaceutically acceptable salt
- 4 thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁,
- 5 CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$,
- where R_7 is an alkyl, cycloalkyl or alkenyl group
- 7 containing 1 to 5 carbons, R_0 is an alkyl group of 1
- 8 to 10 carbons or trimethylsilylalkyl where the alkyl
- group has 1 to 10 carbons, or a cycloalkyl group of
- 5 to 10 carbons, or R₈ is phenyl or lower
- 11 alkylphenyl, R_9 and R_{10} independently are hydrogen,
- an alkyl group of 1 to 10 carbons, or a cycloalkyl
- group of 5-10 carbons, or phenyl or lower
- 14 alkylphenyl, R₁₁ is lower alkyl, phenyl or lower
- alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent
- 16 alkyl radical of 2-5 carbons.
- 7. A process in accordance with Claim 6 where
- the RAR_{α} specific or selective retinoid compound is
- in accordance with formula (i).
- 20 8. A process in accordance with Claim 7 where
- in the formula of the RAR_{α} specific or selective
- retinoid compound X_1 is $[C(R_1)_2]_n$ and n is 1.
- 23 9. A process in accordance with Claim 8 where
- 24 in the formula of the RAR_{α} specific or selective
- 25 retinoid compound Y is phenyl.
- 26 10. A process in accordance with Claim 6 where
- 27 the RAR_{α} specific or selective retinoid compound is
- 28 in accordance with formula (ii).
- 29 11. A process in accordance with Claim 10 where
- $_{30}$ in the formula of the RAR $_{\alpha}$ specific or selective
- 31 retinoid compound Y is phenyl.
- 12. A process of administering to a mammal a
- 33 retinoid compound which binds specifically or
- 34 selectively to a RAR_{α} retinoid receptors in

- preference over RAR, and RAR, retinoid receptors, for
- 2 the purpose of treating or preventing a disease or
- 3 condition which is responsive to treatment by RAR_a
- 4 specific or selective retinoid agonists, the
- 5 retinoid compound being specific or selective for
- $_{6}$ $^{\circ}$ RAR_{α} retinoid receptors in preference over RAR_{β} and
- 7 RAR_r retinoid receptors when in a binding assay the
- 8 K_d value of binding to RAR_a receptors is
- 9 approximately 500 times smaller than the K_d value for
- 10 binding to RARs and RARr retinoid receptors.
- 11 13. A process in accordance with Claim 12 where
- the RAR_a specific or selective retinoid compound is
- administered to a mammal for the treatment or
- prevention of the disease or condition selected from
- actinic keratoses, arsenic keratoses, inflammatory
- and non-inflammatory acne, psoriasis, ichthyoses,
- 17 eczema, atopic dermatitis, Darriers disease, lichen
- 18 planus, glucocorticoid damage, topical microbial
- infection, skin pigmentation, age and photo damage
- 20 to the skin, premalignant and malignant
- 21 hyperproliferative diseases, Kaposi's sarcoma,
- 22 diseases of the eye, proliferative vitreoretinopathy
- 23 (PVR), retinal detachment, dry eye and other
- 24 corneopathies, cardiovascular diseases,
- 25 dyslipidemias, prevention of post-angioplasty
- 26 restenosis, diseases associated with human papilloma
- 27 virus (HPV), inflammatory diseases,
- 28 neurodegenerative diseases, improper pituitary
- 29 function, insufficient hair growth, diseases
- 30 associated with the immune system, and wound
- 31 healing.
- 14. A process in accordance with Claim 13 where
- 33 the RAR_{α} specific or selective retinoid compound is
- 34 administered to a mammal for the treatment or

prevention of the disease or condition selected from

```
acute monocytic leukemia, cervical carcinoma,
 2
     myeloma, ovarian carcinomas, head and neck
 3
     carcinomas, proliferative vitreoretinopathy (PVR)
     and age related macular degeneration (AMD).
          15. A process in accordance with Claim 13 where
 6
    the RAR_{\alpha} specific or selective retinoid compound has
 7
    the formula (i) or the formula (ii)
 8
 9
10
11
                       (H_2)m
                                                   (R_2)m
12
13
     (R<sub>3</sub>)o
                                                           Y(W2)r
14
15
               (W_1)p
                                           (W<sub>3</sub>)p
16
17
18
19
20
         formula (i)
21
                                               formula (ii)
    where X_1 is 0 or X_1 is [C(R_1)_2]_n where n is an integer
22
    between 0 and 2:
23
         R_1 is independently H or alkyl of 1 to 6
24
    carbons;
25
         \mathbf{R}_{\mathbf{z}} is independently hydrogen, or lower alkyl of
26
    1 to 6 carbons:
27
         R3 is hydrogen, lower alkyl of 1 to 6 carbons or
28
    F;
29
         m is an integer having the value of 0 - 5;
30
         o is an integer having the value of 0 - 4;
31
         p is an integer having the value of 0 - 2;
32
         r is an integer having the value 0 - 2;
33
         X, is N or CH;
34
```

1

```
Y is a phenyl or naphthyl group, or heteroaryl
1
    selected from a group consisting of pyridyl,
2
   thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
   thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said
4
   phenyl, naphthyl and heteroaryl groups being
   optionally substituted with one or two R, groups;
        W<sub>1</sub> is a substituent selected independently from
7
   the group consisting of F, Br, Cl, I, fluoro
   substituted C_{1-6} alkyl, NO_2, and OH, with the provisos
9
   that:
10
              when the compound is in accordance with
11
   formula (i) and Z is O then the sum of p and r is at
12
   least 1 and W<sub>1</sub> is not a fluoro group in the 3
13
   position of a tetrahydronaphthalene ring;
14
        (ii) when the compound is in accordance with
15
   formula (i) and r is zero and p is 1 and W, is OH
16
17
   then the OH group is positioned \alpha to the L group;
        W2 is a substituent selected independently from
18
   the group consisting of F, Br, Cl, I, fluoro
19
   substituted C_{1-6} alkyl, NO_2, and OH;
20
        W, is a substituent selected independently from
21
   the group consisting of F, Br, Cl, I, C, alkyl,
22
   fluoro substituted C1-6 alkyl, NO2, and OH with the
23
   proviso that when the compound is in accordance with
24
   Formula 2 and X2 is CH and r is 0 then p is not 0 and
25
   at least one W, group is not alkyl;
26
        L is -(C=Z)-NH- or -NH-(C=Z)-
27
        Z is 0 or S, and
28
        B is COOH or a pharmaceutically acceptable salt
29
   thereof, COOR, CONR, R10, -CH2OH, CH2OR, CH2OCOR,
30
   CHO, CH(OR_{12})_2, CHOR_{13}O, -COR_7, CR_7(OR_{12})_2, CR_7OR_{13}O,
31
   where R_7 is an alkyl, cycloalkyl or alkenyl group
32
   containing 1 to 5 carbons, R, is an alkyl group of 1
33
   to 10 carbons or trimethylsilylalkyl where the alkyl
34
```

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group has 1 to 10 carbons, or a cycloalkyl group of

- $_2$ 5 to 10 carbons, or R_g is phenyl or lower
- alkylphenyl, R_9 and R_{10} independently are hydrogen,
- an alkyl group of 1 to 10 carbons, or a cycloalkyl
- 5 group of 5-10 carbons, or phenyl or lower
- 6 alkylphenyl, R₁₁ is lower alkyl, phenyl or lower
- 7 alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent
- 8 alkyl radical of 2-5 carbons.
- 16. A process in accordance with Claim 15 where the RAR $_{\alpha}$ specific or selective retinoid compound is in accordance with **formula** (i).
- 17. A process in accordance with Claim 15 where 13 the formula the RAR_{α} specific or selective retinoid 14 compound is in accordance with **formula** (ii).
- 18. A process of administering to a mammal a 16 retinoid compound which binds specifically or 17 selectively to a RAR_a retinoid receptors in
- 18 preference over RAR, and RAR, retinoid receptors, for
- 19 the purpose of treating or preventing the disease or
- 20 condition selected from acute monocytic leukemia,
- 21 cervical carcinoma, myeloma, ovarian carcinomas,
- 22 head and neck carcinomas, proliferative
- 23 vitreoretinopathy (PVR) and age related macular
- 24 degeneration (AMD) the retinoid compound being
- specific or selective for RAR_{α} retinoid receptors in
- $_{\rm 26}$ $\,$ preference over ${\rm RAR}_{_{\rm B}}$ and ${\rm RAR}_{_{\rm T}}$ retinoid receptors when
- in a binding assay the K_d value of binding to RAR_{α}
- 28 receptors is approximately 500 times smaller than
- the K_d value for binding to RAR_B and RAR_r retinoid
- 30 receptors, the retinoid compound having the formula
- 31 (i) or the formula (ii)

32 33

34

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2
                                                      (R_2)m
                      (H_2)m
 5
               (W1)p
 7
 8
9
         formula (i)
10
                                             formula (ii)
   where X_1 is 0 or X_1 is [C(R_1)_2]_n where n is an integer
11
    between 0 and 2;
12
         R<sub>1</sub> is independently H or alkyl of 1 to 6
13
    carbons;
14
         R2 is independently hydrogen, or lower alkyl of
15
    1 to 6 carbons;
16
         R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or
17
   F;
18
         m is an integer having the value of 0 - 5;
19
         o is an integer having the value of 0 - 4;
20
         p is an integer having the value of 0 - 2;
21
         r is an integer having the value 0 - 2;
22
         X_2 is N or CH;
23
         Y is a phenyl or naphthyl group, or heteroaryl
24
   selected from a group consisting of pyridyl,
25
   thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
26
   thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said
27
   phenyl, naphthyl and heteroaryl groups being
28
   optionally substituted with one or two R, groups;
        W<sub>1</sub> is a substituent selected independently from
30
   the group consisting of F, Br, Cl, I, fluoro
31
   substituted C_{1-6} alkyl, NO_2, and OH, with the provisos
32
   that:
33
              when the compound is in accordance with
         (i)
34
```

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```
formula (i) and Z is O then the sum of p and r is at
  1
     least 1 and W_1 is not a fluoro group in the 3
  2
     position of a tetrahydronaphthalene ring;
          (ii) when the compound is in accordance with
  4
     formula (ii) and r is zero and p is 1 and W_1 is OH
  5
     then the OH group is positioned \alpha to the L group;
        W2 is a substituent selected independently from
  7
     the group consisting of F, Br, Cl, I, fluoro
  8
     substituted C_{1-6} alkyl, NO_2, and OH;
          \mathbf{W}_3 is a substituent selected independently from
 10
     the group consisting of F, Br, Cl, I, C_{1-6}alkyl,
 11
     fluoro substituted C_{1-6} alkyl, NO_2, and OH with the
 12
    proviso that when the compound is in accordance with
 13
    Formula 2 and X_2 is CH and r is 0 then p is not 0 and
 14
    at least one W3 group is not alkyl;
 15
         L is -(C=Z)-NH- or -NH-(C=Z)-
 16
         Z is 0 or S, and
 17
         B is COOH or a pharmaceutically acceptable salt
18
    thereof, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>,
19
    CHO, CH(OR_{12})_2, CHOR_{13}O, -COR_7, CR_7(OR_{12})_2, CR_7OR_{13}O,
20
    where R_7 is an alkyl, cycloalkyl or alkenyl group
21
    containing 1 to 5 carbons, R_8 is an alkyl group of 1
22
    to 10 carbons or trimethylsilylalkyl where the alkyl
23
    group has 1 to 10 carbons, or a cycloalkyl group of
24
    5 to 10 carbons, or R_s is phenyl or lower
25
    alkylphenyl, R_9 and R_{10} independently are hydrogen,
26
    an alkyl group of 1 to 10 carbons, or a cycloalkyl
27
    group of 5-10 carbons, or phenyl or lower
28
    alkylphenyl, R11 is lower alkyl, phenyl or lower
29
    alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent
30
   alkyl radical of 2-5 carbons.
31
```

19. A process in accordance with Claim 18 where the RAR $_{\alpha}$ specific or selective retinoid compound is in accordance with **formula** (i), and Y is phenyl.

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20. A process in accordance with Claim 19 where the
   RAR, specific or selective retinoid compound is
 2
    selected from the group consisting of:
 3
        ethyl 2-fluoro-4-[(5',6',7',8'-tetrahydro-
 4
   5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
 5
   nzoate:
 6
        2-fluoro-4-[(5',6',7',8'-tetrahydro-
7
   5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
   nzoic acid;
9
        ethyl 2-fluoro-4-[(5',6',7',8'-tetrahydro-4'-
10
   bromo-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbam
11
   oyl]benzoate;
12
        2-fluoro-4-[(4'-bromo-5',6',7',8'-tetrahydro-
13
   5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
14
   nzoic acid;
15
        ethyl
16
   2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman
17
   -6'-yl)carbamoyl]benzoate;
18
19
   2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman
20
   - 6'-yl)carbamoyl]benzoic acid;
        ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
22
   trifluoromethylchroman-6'-yl)carbamoyl] benzoate;
23
        2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
24
   trifluoro-methylchroman-6'-yl)carbamoyll benzoic
25
   acid;
26
        ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
27
   azidochroman-6'-yl)carbamoyl]benzoate;
28
        2-fluoro-4-[(2',2',4',4'-tetramethy1-8'-
29
   azidochroman- 6'-yl)carbamoyl]benzoic acid;
30
        ethyl 2-fluoro-4-[(2', 2', 4', 4'-tetramethyl-
31
   8'-iodochroman-6'-y1)carbamoy1]benzoate;
32
        2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
33
   iodochroman-6'-yl)carbamoyl]benzoic acid;
34
```

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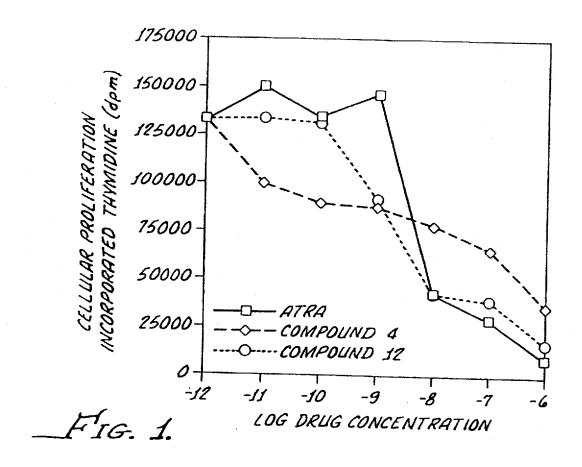
Z.J. SMITTASAK

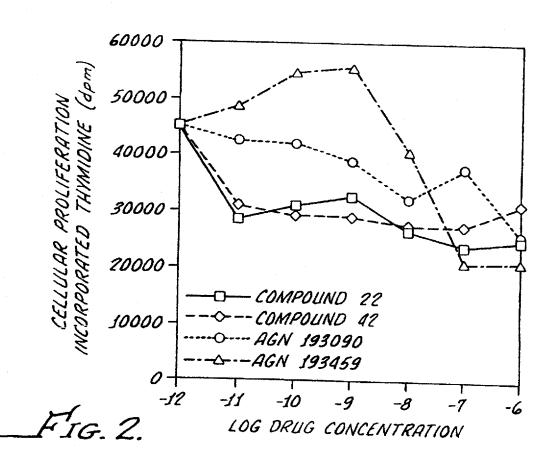
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ethyl 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
 1
    tetramethyl-2-naphthalenyl)thiocarbamoyl]benzoate,
2
    and
        4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
4
   tetramethylnaphthalen-2'-yl)thiocarbamoyl]benzoic
   acid.
             A process in accordance with Claim 18 where
7
   the RAR_{\alpha} specific or selective retinoid compound is
   in accordance with formula (ii), and Y is phenyl.
9
        22. A process in accordance with Claim 19 where
10
        RAR_{\alpha} specific or selective retinoid compound
   the
11
   is:
12
        ethyl 2-fluoro-4-[(2'6'-di-tert-butylpyrid-4'-
13
   yl)carbamoyl]benzoate, or
14
        2-fluoro-4-[(2',6'-di-t-butylpyrid-4'-
15
```

yl)carbamoyl]benzoic acid.

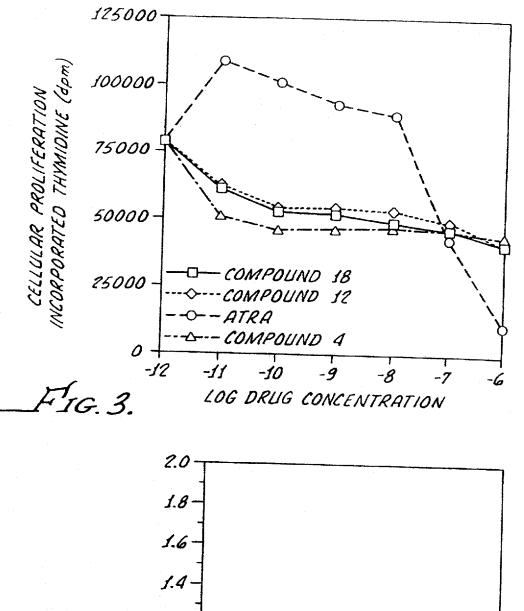
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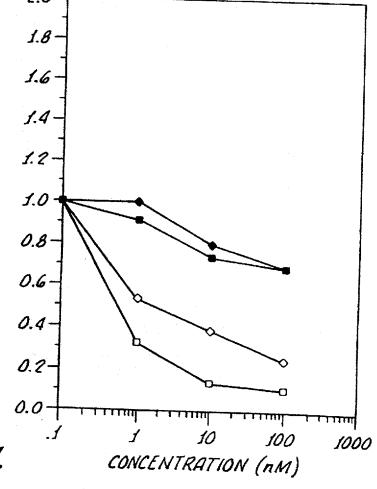
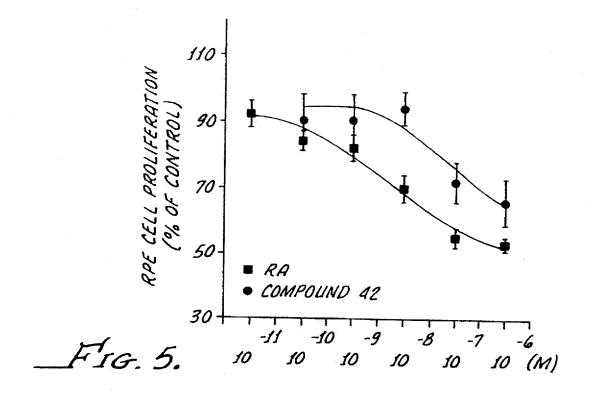
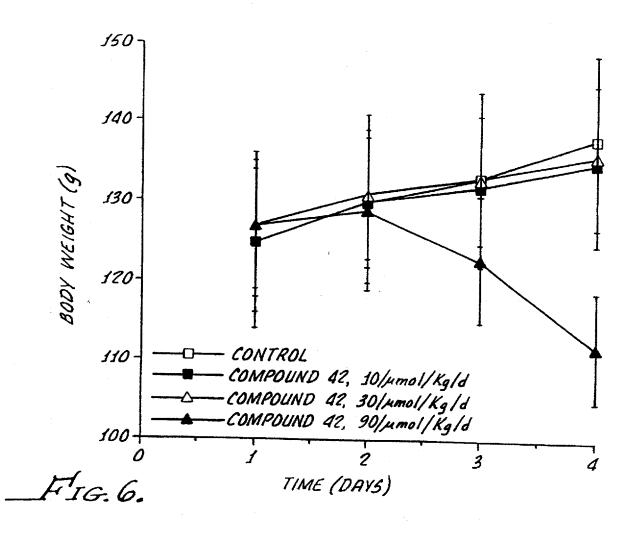


FIG. 4.

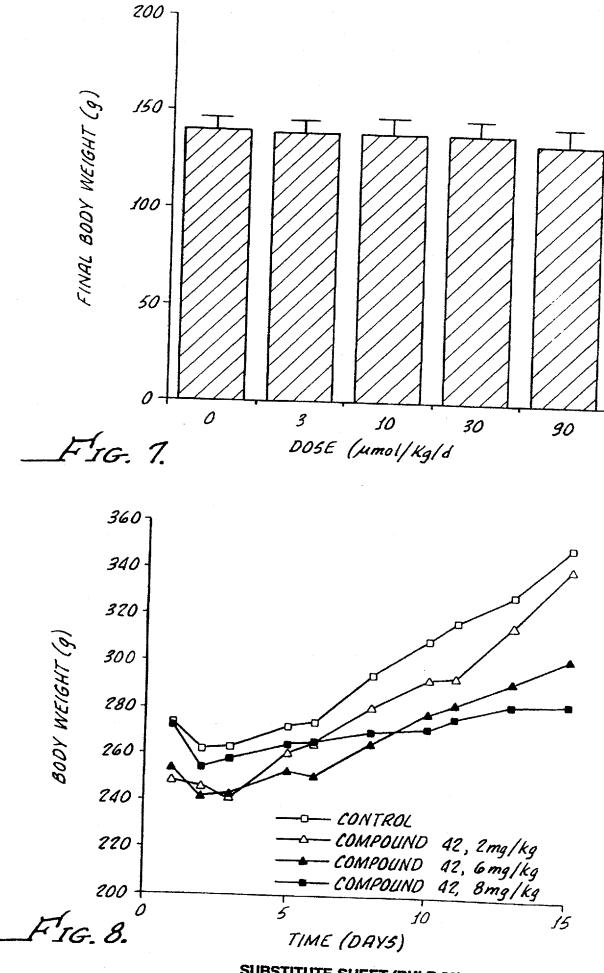
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